

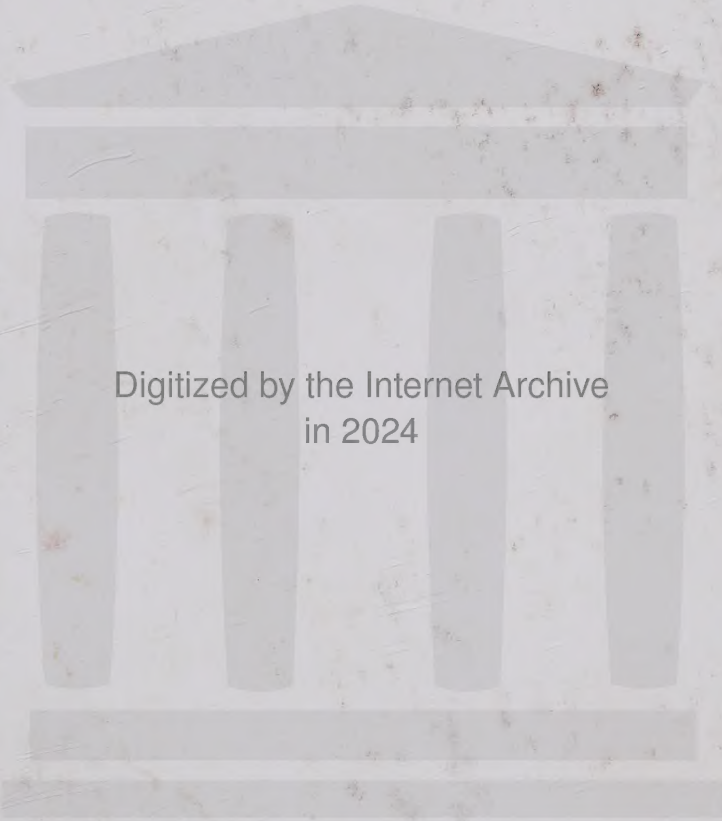
**THE
MEDICAL CLINICS
OF NORTH AMERICA**



**DISEASES OF THE
RESPIRATORY TRACT**

**VOLUME 48 — NUMBER 4
JULY, 1964**





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THE
MEDICAL CLINICS
OF NORTH AMERICA

DISEASES OF THE RESPIRATORY TRACT

MATTHEW B. DIVERTIE, M.D.

W. SPENCER PAYNE, M.D.

Guest Editors

Volume 48 — Number 4

JULY, 1964

W. B. SAUNDERS COMPANY — Philadelphia & London

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The following information is published in accordance with the requirements of the United States Postal Code.

The Medical Clinics of North America is published every other month by W. B. Saunders Company, West Washington Square, Philadelphia 5, Pennsylvania at Hampton Road, Cherry Hill, New Jersey. Subscription price is \$18.00 per year. Second-class postage paid at Haddonfield, New Jersey.

This issue is Volume 48, Number 4.

The editor of this publication is Dwight J. Hotchkiss, W. B. Saunders Company, West Washington Square, Philadelphia 5, Pennsylvania.

Library of Congress catalog card number 17-28505

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SYMPOSIUM ON DISEASES OF THE RESPIRATORY TRACT

Foreword

Cycles of interest and progress in medicine change from time to time in every field, but the same familiar diseases remain to trouble both patient and physician. In the field of pulmonary disease, the challenge of the future greatly outweighs the considerable accomplishments of the past. The present moment, where accomplishment and challenge touch, is the vantage point of this consideration of respiratory disorders.



MATTHEW B. DIVERTIE



W. SPENCER PAYNE

Tuberculosis and the acute bacterial pneumonias give no sign of being eradicated but they have yielded substantially to chemotherapy, although ineffectual treatment has produced complication rather than simplicity in some cases. Chronic respiratory insufficiency is one of the major causes of protracted loss of earning power in the present day, and the management of emphysema in our mobile and complex society frequently requires answers to specific problems of surgical treatment or transportation of the patient. The early diagnosis of pulmonary malignancy affects survival favorably and is aided by clinical awareness of less common manifestations of these tumors and by use of newer diagnostic tools. The responses of the lung to systemic processes and to extracorporeal circulation have stimulated the attention of many, and the basic science fields are being explored for information of potential value in explaining their causes. From this area, too, assistance in the accomplishment of lung transplantation is being sought with particular reference to rejection mechanisms.

We are indebted to our colleagues for the reviews of these problems which are set out in the following pages, and we hope that they will prove a stimulus to many and a service to all who read them.

MATTHEW B. DIVERTIE, M.D.
W. SPENCER PAYNE, M.D.

An Anniversary—and a Note of Appreciation

HERBERT W. SCHMIDT, M.D.

MATTHEW B. DIVERTIE, M.D.

The year 1964 is being celebrated in Rochester, Minnesota, as the centennial of the two brothers (born in 1861 and 1865) who founded the Mayo Clinic in this town, and the beginning of the fiftieth year of the establishment of the Mayo Foundation for Medical Education and Research. From their earliest days in practice, the Mayos took considerable interest in intrathoracic disease; and in 1894 Dr. William J. Mayo described three cases of esophageal stricture which he had seen. Five years later he reported on the use of esophagoscopy examination and the treatment of foreign bodies and lye strictures of the esophagus. Neither of these procedures nor the retrograde approach, which he favored, were innovations of his own; but his interest in esophageal disease continued as the practice of thoracic medicine and surgery at the Mayo Clinic expanded with the years.

His brother, Dr. Charles H. Mayo, reported in 1910 his excision of eight pharyngeal diverticula without mortality. All had been removed by the one-stage method. It was not until the middle 1920's, however, that a section devoted to thoracic surgery came into existence as we know it today at the Mayo Clinic. The fortunate choice of Dr. Stuart W. Harrington as its head enabled it to grow and develop soundly. He was later joined by Dr. O. T. Clagett, and the two of them made major contributions to the problems and techniques of their specialty. A wide experience was gained in the difficult surgical problems involved in treatment for mediastinal tumors, tumors of the lung, and esophageal diseases; and between them they fashioned a solid foundation upon which their successors might build securely.

One of the earliest associates of the Mayo Clinic was Dr. Henry S. Plummer, who in 1908 reviewed his experience with 40 cases of achalasia of the esophagus which he had treated by the passage of a thread and the introduction of dilators and a hydrostatic bag. This was to be the method

of choice for many years, until surgical treatment for this condition became safe. Although interested in many other diseases, Dr. Plummer continued to study disorders of the esophagus throughout the rest of his medical career.

The bronchoscope had been available for as long as the roentgen ray and had been used for many years in dealing with foreign bodies; but in company with others in medical centers elsewhere, Dr. Porter P. Vinson provided enthusiastic stimulus to its use in the diagnosis of carcinoma of the lung. In 1932 he described his experience with it at the Mayo Clinic.

The newly formed section devoted to medical disease of the chest was fortunate in having men of the caliber of Dr. Willis S. Lemon, Dr. Herman J. Moersch, and Dr. Harry G. Wood. Dr. Moersch made major contributions in the techniques of endoscopy and in 1940 introduced the method of local injection of esophageal varices through an esophagoscope.

It is less than 20 years since effective chemotherapy has become available for the treatment of tuberculosis. In April, 1944, Dr. H. Corwin Hinshaw and Dr. William H. Feldman, of the sections concerned with medical chest disease and comparative pathology, respectively, began their experiments using streptomycin against the tubercle bacillus in guinea pigs. These proved successful, and its use was extended to patients at nearby Mineral Springs Sanatorium. Two years later the results of their successful work were reported at a meeting of the National Tuberculosis Association and subsequently they were amply confirmed by others. This was the first clinical use of an effective chemotherapeutic agent against tuberculosis.

In this centennial year it seems especially fitting that those of us who have contributed to this present volume should pay our respects and tribute to those in whose footsteps we follow.

The Diagnosis and Management of Acute Infectious Pneumonia

GEORGE W. MORROW, JR., M.D.

HOWARD A. ANDERSEN, M.D.

JOSEPH E. GERACI, M.D.

In our practice, the major diagnostic problem raised by infectious pneumonia is to determine whether the pathogens are bacteria, pleuropneumonia-like organisms, or viruses; so this discussion is concerned principally with the diagnosis of these types of the disease and the therapy dependent on it. Rickettsial organisms and fungi appear as pneumonic pathogens, but less frequently. Pneumonia encountered as the initial finding in certain generalized infections warrants special consideration and will be dealt with only briefly here.

CHARACTERISTICS OF INFECTIOUS AGENTS

The organisms most likely to produce primary infectious pneumonia are listed in Table 1.

Bacterial Organisms

Pneumococci, still the most common cause of bacterial pneumonia, usually are responsible for a lobar reaction. Common initial symptoms are productive cough, pleuritic pain, and high fever. A rapid response to penicillin therapy is usual.

Staphylococcal pneumonia, most often lobular, is not so clear-cut in regard to symptoms. Cough may be nonproductive initially, and response to antibiotic therapy varies in proportion to the resistance of the causative organism. The incidence of staphylococcal pneumonia is said to have risen remarkably in recent years. The increase may be attributable in part to staphylococcal superinfection in patients hospitalized for other illnesses. This potentiality is especially important in viral pneumonia, for in such

Table 1. *Most Common Etiologic Agents of Primary Infectious Pneumonia*

Bacteria	Pleuropneumonia-like Organisms
Pneumococcus	Eaton agent
Staphylococcus	Viruses
Streptococcus	Influenza (types A, B)
Hemophilus influenzae	Adenovirus (APC)
Klebsiella pneumoniae	Parainfluenza (types 1, 2, 3)
(Friedländer's bacillus)	Respiratory syncytial virus
Mycobacterium tuberculosis	Unidentified

cases secondary pulmonary infection by staphylococci is a major cause of death.

Streptococcal infection should be strongly suspected when pneumonia is accompanied by purulent pharyngitis or painful anterior cervical adenopathy. Pleural effusion is a common complication.

Hemophilus influenzae, although capable of producing primary pneumonia, more often is a secondary invader after other organisms have initiated the pulmonary process. Infrequently, Klebsiella pneumoniae (Friedländer's bacillus) causes pneumonia. The reaction typically is lobar, with an affinity for the upper part of the lungs of debilitated patients. Tuberculosis also is to be suspected in pneumonia involving the upper lobes of the lung, and suspected more strongly if there is a history of ill health prior to onset of the pneumonia or if anticipated clinical improvement does not occur.

Pleuropneumonia-like Organisms

Eaton agent has been identified recently as belonging among the pleuropneumonia-like organisms. This group of the genus *Mycoplasma* shares characteristics with both viruses and bacteria. Eaton agent (or *Mycoplasma pneumoniae*, as proposed by Chanock and associates)^{1, 2} has a particle size estimated² as 180 to 250 m μ —a magnitude similar to that of viruses. The organism apparently has enzyme systems as do bacteria, because growth is sustained on cell-free media and pneumonia produced by this agent is said to respond to antibiotic therapy.² But except for an increased incidence of myringitis,³ Eaton-agent infection presents a clinical pattern as yet indistinguishable from that of viral disease.

Viral Organisms

Proved viral pneumonia has been due, in most cases, to the adenoviruses or to influenza viruses, types A and B. In the para-influenzal group, type 3 is most likely to produce pneumonia in adults. Pneumonia due to respiratory syncytial virus shows a predilection for children. Some clinical characteristics have been delineated during outbreaks of illness caused by these viruses. Among sporadic cases, however, it is most difficult to diagnose an illness as being due to a specific virus on clinical grounds alone.

During World War II the term "primary atypical pneumonia" was used to designate a patchy infiltrate of the lung not responding to antibiotic therapy. As yet, its etiology is not clearly delineated. Some investigators believe that it is caused by a single organism, Eaton agent; others believe it is caused by many viruses, some unidentified. We no longer use the term because of the continued disagreement regarding etiology and our observations that many of the primary pneumonias do not respond to antibiotic treatment and their course and manifestations suggest a viral basis. Therefore this type of pneumonia is no longer "atypical," but rather to be expected.

Among 290 cases of nonbacterial pneumonia in marine recruits, Kingston and associates found Eaton agent in 45.9 per cent. They were unable to identify any pathogens in 42.1 per cent, but thought that possibly those were viral. Our attempts to determine the specific viruses responsible for our cases of pneumonia have been even less rewarding. This poses the question of how to establish the cause of primary infectious pneumonia.

DIAGNOSIS

Laboratory Methods for Early Diagnosis; Limitations

Culture of representative specimens of sputum and blood collected prior to antibiotic therapy is the recognized screening technique for all cases of pneumonia. It provides the opportunity of establishing a bacterial diagnosis usually in 24 to 48 hours. Eaton agent may be identified by culturing on enriched agar the material obtained by throat swabs. Colonies of Eaton agent are recognized by their ability to produce clear (beta) hemolysis of mammalian red blood cells.³ But although this method seems specific for Eaton agent, identification requires no less than four to six days after inoculation.

The early diagnosis of viral infections remains in the investigative stage, but the technique for fluorescent staining of antibodies as described by Liu and colleagues appears promising. Currently, however, viral diagnosis depends on paired serum determinations—that is, finding a rising viral-antibody titer when acute-phase serum obtained as soon as possible after onset of illness is compared with convalescent-phase serum obtained three or more weeks after the onset. In our experience, this determination affords a diagnosis in far less than 25 per cent of the paired serum specimens submitted; and even then the diagnosis arrives long after the pneumonia has run its course.

These limitations mean that, unless the pneumonia is bacterial, an early precise diagnosis is not to be obtained from use of commonly available laboratory techniques. For the present, we must turn to other available clinical and laboratory aids for whatever help they can give.

Aids to Timely Differentiation of Type of Infection

ROENTGENOGRAPHY. Roentgenographic findings are necessary to confirm the diagnosis of pneumonia and may give some indication as to the type of pneumonia present. In general, infiltration of an entire segment or lobe of the lung suggests a bacterial etiology, and patchy infiltration suggests infection by a virus or Eaton agent. Nevertheless, we have seen viral lobar pneumonia and certainly bacterial bronchopneumonia. For these reasons, we have been unable to establish a diagnostic roentgenographic pattern for either viral or Eaton-agent pneumonia.

A diagnosis of bacterial pneumonia is usually justified when the roentgenogram reveals cavitation within an area of pulmonic infiltration or when bronchopleural fistula or pneumatocele is present. We have observed extensive pleural effusion only in bacterial disease.

Therefore, though certain roentgenographic characteristics help to identify bacterial infections, in most cases the roentgenograms of the thorax merely confirm the presence of pneumonia.

CLINICAL PATTERNS AND CORRELATIONS. Viral and Eaton-agent infections demonstrate similar clinical patterns. Certain clinical characteristics, however, help differentiate bacterial processes from these nonbacterial infections. Bacterial pneumonia classically starts with a productive cough. In viral and Eaton-agent pneumonia, cough ordinarily is absent initially; if present, it usually is dry and irritating, while the main complaints are headache, myalgia, malaise, and fever. Hemoptysis is frequent in bacterial pneumonia and the sputum is bright red to rust-colored; in viral and Eaton-agent pneumonia, hemoptysis is less frequent and the sputum is almost always bright red. Chest pain is common in bacterial disease, presents at the onset of illness, and is sharply localized and pleuritic in type; it is less common in viral and Eaton-agent disease, usually occurs two or more days after onset of illness, and may be of two types—diffuse and aching, or pleuritic. The pulse rate is rapid and correlates with the level of fever in bacterial disease; in viral and Eaton-agent disease it tends to be slower than expected, since it is not unusual for a patient with a temperature of 104°F. to have a pulse rate of 100.

Usually in bacterial disease the response to therapy is favorable, and prompt recovery is expected if a positive sputum culture is obtained and an appropriate antibiotic is administered. Since no agents of proved viricidal activity are commercially available at present, patients with viral pneumonia usually have a sustained fever for five to seven days, which resolves by lysis with slow recovery, the malaise lingering for two or more weeks. Although the natural course of Eaton-agent pneumonia is similar to that of viral pneumonia, it may be altered favorably by appropriate antibiotic therapy.

Conjunctivitis and palatal petechiae occur frequently in viral disease but rarely in bacterial or Eaton-agent disease. In viral and Eaton-agent

pneumonia, pulmonary findings on physical examination often cannot be correlated with roentgenographic changes; at the onset, rales may be present though roentgenographic changes are minimal; later, roentgenographic changes may exceed the physical findings, or auscultation of the lungs may give normal findings and yet roentgenograms may disclose an unsuspected and often extensive pneumonia. In bacterial pneumonia, rales and roentgenographic changes usually appear simultaneously. Consolidation is a feature of pneumonia, whether bacterial, viral, or Eaton agent; but it is usually less extensive in the viral and Eaton-agent forms. Pleural effusion is common and often extensive in bacterial disease, but rare and minimal in viral and Eaton-agent disease.

LABORATORY AIDS. During World War II the "atypical pneumonias" were characterized by leukopenia and relative lymphocytosis. Such a finding is not common today. Now in viral and Eaton-agent pneumonia the leukocyte count usually is normal if increased it seldom exceeds 15,000 per cubic millimeter of blood, and neutrophils frequently comprise 90 per cent of the leukocytes. In bacterial pneumonia the leukocyte count ordinarily is increased, often exceeding 15,000; and usually the percentage of neutrophils is increased. Therefore, abnormalities in total number as well as in differential count are not so helpful in diagnosis as originally thought. This statement applies also to the sedimentation rate of erythrocytes, which is elevated in bacterial and in viral and Eaton-agent pneumonia; however, the increase is more likely to be of significant proportions in viral disease, where it often exceeds 100 mm. in one hour (Westergren method).

Cold agglutinins are detected occasionally in several types of illness, but their presence in Eaton-agent infection is regular enough to be helpful in diagnosis. For an Eaton-agent diagnosis to be suspected, at least a fourfold increase in the titer of cold agglutinins must occur during the acute stage of the illness. The result of the cold agglutinin-test is positive in about 50 per cent of Eaton-agent cases.⁶ Correlation appears to exist between production of cold agglutinins and the clinical course, the test becoming positive more frequently and demonstrating higher titers in the cases that are more severe clinically.

Streptococcus MG titers were first observed in viral pneumonia by Thomas and colleagues in 1945. Subsequent studies indicate that this bacterium plays no etiologic role in viral pneumonia, but a fourfold rise in serum titers against it carries the same diagnostic significance as that ascribed to cold agglutinins.

HISTOLOGIC FEATURES. In bacterial pneumonia the pulmonary alveoli are filled with exudate composed most often of polymorphonuclear leukocytes and fibrin, while the alveolar septa remain thin-walled. Bronchitis and tracheitis occur, and foci of necrosis may develop. The distribution of the inflammation is lobar or lobular.

In viral pneumonia the inflammation is interstitial, as evidenced by thickening of the alveolar septa. The alveoli may be partially filled with

fibrin-poor exudate and leukocytes (usually mononuclear) and often are lined by a red-staining hyaline membrane. Tracheitis, bronchitis, and bronchiolitis are common; but necrosis is rare. The inflammation usually assumes a lobular distribution.

Eaton-agent pneumonia, in the few postmortem studies reported, has demonstrated a histologic pattern similar to that observed in viral pneumonia.

PHYSIOLOGIC CONSIDERATIONS

Symptoms and prognosis are closely related to the level of arterial oxygen saturation. When the oxygen saturation drops from a normal of 95 per cent into the vicinity of 85 per cent, the accompanying hypoxia produces sleeplessness, delirium, cyanosis, and dyspnea. The severity of these symptoms varies directly with the degree of hypoxia. High mortality is associated with any arterial oxygen-saturation level lower than 80 per cent.⁹

The two major causes of hypoxia in pneumonia are shallow breathing and the passage of blood through unaerated portions of the lung. Shallow breathing may result from pleuritic pain, exhaustion of respiratory muscles, or depression of the respiratory center from hypoxia itself. Hypoxia may occur during the early, "red hepatization" stage of lobar pneumonia because, though the arterioles remain patent, the alveolar exudate impairs aeration. It is less likely to occur during the later, "gray hepatization" stage because the arterioles traversing the unaerated lobe become obliterated. In bacterial lobular pneumonia, the blood vessels remain patent and hypoxia tends to occur at all stages; in viral and most rickettsial pneumonias, hypoxia is caused primarily by the marked swelling of the alveolar septa, which together with the hyaline membrane form an alveolar-capillary block that prevents free diffusion of oxygen from the alveoli to the capillaries.

Finally it should be emphasized that the extent of pulmonary involvement has a decided bearing on the degree of hypoxia attained. If the pneumonia involves several lobes or if the uninvolved lung has pre-existing damage, as from emphysema, the hypoxia may become severe.

PNEUMONIA IN INFECTIOUS SYSTEMIC DISEASE

One should remember that pneumonia can be a manifestation of some systemic diseases produced by infectious agents. Hence brucellosis and typhoid fever are diagnostic possibilities for any patient who has had contact with fomites, as is tularemia for those who have handled wild animals. Psittacosis is contracted from psittacine birds such as parakeets or parrots, and ornithosis may be spread by most barnyard fowl as well

as by pigeons and pheasants. Q fever should be remembered, especially if the patient works in a meatpacking plant. In its endemic areas, Rocky Mountain spotted fever must be considered, particularly after tick bite. Viral pneumonia complicating measles is most common in children; viral pneumonia complicating chickenpox seems to have a special affinity for adults, and it carries a significant mortality. Certain fungal diseases (histoplasmosis, coccidioidomycosis) may present as acute pneumonia.

MANAGEMENT

Antibiotic Therapy

The antimicrobial management of the pneumonias depends on the clinician's combination of acumen and thorough knowledge of the therapeutic and toxic potentials of the antimicrobial agents. We shall summarize here some views regarding the use of individual antimicrobial agents in the types of pneumonia to be indicated. Detailed descriptions of these agents together with dosage schedules may be found in the article by Geraci and associates.

In pneumococcal and streptococcal infections, penicillin G remains the agent of choice. Erythromycin may be substituted if the patient is allergic to penicillin.

In staphylococcal pneumonia, if the organism is sensitive to penicillin G, then aqueous crystalline penicillin G is the agent of choice. Infections caused by staphylococci resistant to penicillin G are treated with one of the semisynthetic penicillins. Parenteral therapy with methicillin (Staphicillin) is best initially; sodium oxacillin (Prostaphlin) is reserved for oral administration after the infection has been brought under control. Since penicillin G and the semisynthetic penicillins are cross-allergenic, the latter agents cannot be used in patients who previously have had a serious untoward reaction to penicillin G. In patients with mild to moderate infections who are allergic to penicillin G, erythromycin or novobiocin may be substituted; but in the moderate to severe infections and those caused by strains resistant to penicillin G, vancomycin and kanamycin are the agents of second and third choice. Not given

In infections due to *H. influenzae*, *K. pneumoniae*, or brucellar organisms, combined tetracycline-streptomycin therapy is effective. Streptomycin alone suffices in infections due to *Pasteurella tularensis*, as this species remains uniformly sensitive to it. Chloramphenicol continues as the drug of choice for infections due to *Salmonella typhosa*. Tetracycline is used in rickettsial infections such as Rocky Mountain spotted fever and Q fever, and also in psittacosis and ornithosis.

Eaton-agent pneumonia has been reported to respond to treatment with the tetracyclines and also to streptomycin.^{2, 6} Currently no commercial antimicrobial agent with viricidal properties is available.

For use in histoplasmosis, coccidioidomycosis, and other fungal pneumonias, the agent of choice is amphotericin B (Fungizone). For tuberculous pneumonia the combination of streptomycin and isoniazid is first choice, with para-aminosalicylic acid available as a substitute for either agent if allergy or drug resistance exists or develops.

Many investigators have criticized attempts to provide antimicrobial coverage of all pneumonias. We heartily concur in this view. In our experience, many of the primary pneumonias do not respond to antibiotic therapy; and the course and findings in these infections suggest a viral cause. Therefore one should always try to differentiate between viral, Eaton-agent, and bacterial disease and—if the illness is not critical—should await reports on microbiologic studies before considering antimicrobial therapy.

One important exception, however, is fulminating staphylococcal pneumonia, which may be indistinguishable from severe viral pneumonia in the first 48 hours. In such cases sputum is scanty, the patient shows cyanosis and dyspnea far out of proportion to roentgenographic or auscultatory findings, and not infrequently death supervenes before a definite diagnosis can be established. We believe that patients so gravely affected should be presumed to have a staphylococcal infection; hence, immediately after procuring blood for culture and sputum for both a gram-stained smear and culture, we treat such patients empirically with broad-spectrum antibiotic coverage calculated to kill strains of staphylococci resistant to penicillin G. If the stained smear made from sputum shows both gram-positive cocci and gram-negative organisms, to give large doses of penicillin G intravenously and kanamycin intramuscularly is appropriate. If only gram-positive cocci are noted, large doses of penicillin G and methicillin can be administered together until results of the cultures and in vitro studies are reported, and then the appropriate course of treatment can be continued.⁴ If the patient is not critically ill, we administer antimicrobial drugs only upon clinical or laboratory evidence of infection due to susceptible pathogens.

We avoid use of the tetracycline drugs except in situations for which other drugs are known to be less effective (Eaton-agent infection, psittacosis, and infections due to rickettsial or brucellar organisms, *K. pneumoniae*, and occasionally *H. influenzae*). This practice is based on our experience and that of others⁵ that secondary staphylococcal invasion is more likely to occur in patients receiving tetracycline or allied agents that suppress the gram-negative elements of the normal body flora. In viral pneumonia, secondary infection is best prevented by confinement of the patient at home, if feasible, since hospitalization may provide contact with virulent bacteria and the possibility of superinfection.

Supportive Therapy

The following measures are aimed at supporting the patient through

the period of hypoxia until aeration of the diseased lung begins. Oxygen therapy is specific for dyspnea, though unfortunately its benefit in severe viral pneumonia is limited, apparently because of the phenomenon of alveolar-capillary block. Prolonged dyspnea may lead to exhaustion, and in this event a tank resuscitator may provide lifesaving support. Excessive pulmonary secretions, if not raised by coughing, must be removed by catheter suction, either through the nasopharyngeal route or by tracheostomy if necessary. For the critically ill patient, tracheostomy should be considered early, before exhaustion and irreversible hypoxia supervene.

Steroid therapy may help in tuberculous pneumonia (when combined with administration of antituberculous drugs) and in bronchospasm or asthma complicating pneumonia; it is also worthy of trial in desperate illness when the phenomenon of alveolar-capillary block is suspected.

Close observation for congestive heart failure and for urinary retention is important, particularly in the aged. The importance of satisfactory nutrition and hydration is well appreciated.

PROGNOSIS

Pneumococcal pneumonia still causes significant mortality, particularly when blood cultures are positive. Staphylococcal pneumonia was the leading cause of death in many areas during the recent outbreak of Asian-strain influenza. Eaton-agent pneumonia has not been proved fatal in our limited experience, but this potential may be demonstrated when a diagnostic method for early identification becomes available as a common laboratory procedure.

Viral pneumonia, in most cases, is a self-limiting disease with complete recovery. The concept that it may by itself be fatal has been slow to materialize, but now there is little doubt that it can be the sole mechanism leading to severe hypoxia and death. It appears, however, that most fatalities from viral disease occur because bacterial pneumonia is superimposed on a pre-existing illness. Patients who have congestive heart failure (especially mitral stenosis) or chronic pulmonary disease or are in the third trimester of pregnancy are particularly prone to have pneumonia, often of more than average severity.

Finally, the development of severe dyspnea or cyanosis in any patient with pneumonia reflects a marked degree of hypoxia and therefore justifies the expression of a guarded prognosis.

FOLLOW-UP

We would stress the importance of obtaining serial roentgenograms of the thorax in cases of pneumonia. If the clinical course is unusually

prolonged, or if the pulmonary infiltrate has not resolved completely by the fourth week of illness, one should be alert to the possibility of a tuberculous basis, an associated systemic disease, or an underlying malignant process.

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The Pathology of Dyspnea

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Dyspnea, like headache, is one of the most ubiquitous symptoms in medicine. Just as the extracranial causes of headache are many, so too are the extrapulmonary causes of dyspnea. These range from obesity to the hypoxia of altitude, from metabolic disease to neurosis, and from disease of the central nervous system to anemia. The fact remains, however, that dyspnea is the most common clinical manifestation of pulmonary disease. The pathologic changes of these pulmonary diseases will be the concern of this paper.

Dyspnea has been defined in many ways. A recent book devoted entirely and comprehensively to dyspnea² opens with a chapter concerned only with defining the term. Among these definitions that of Rossier, Bühlmann, and Wiesinger, giving dyspnea as an increase above normal in the work of breathing, whether or not there is a subjective awareness of the increased effort, has the advantage of being succinct and of containing a measurable factor—work. Olsen has considered this and other definitions in detail. However, like the concept of a point in geometry, dyspnea appears to be a basic undefined assumption in clinical medicine.

The physiologic basis for this study of dyspnea will be the simple idea that the prime functions of the lungs are the provision of adequate amounts of oxygen to, and the removal of carbon dioxide from, the blood. When a pathologic process has interfered significantly with these functions, dyspnea occurs.

The anatomy of the lung can be divided, in a functional sense, into a ventilatory system (the bronchial tree down to the respiratory bronchioles and alveolar spaces), a diffusion system (the alveolocapillary membrane), and a perfusion system (the arterial-capillary-venous system). Initially most diseases of the lungs involve only one of these units. Later, however, as the disease progresses, either acutely or chronically, other parts become involved. Emphysema, for instance, may come to involve all of these units.

THE VENTILATORY SYSTEM

The essential lesion in the ventilatory system resulting in dyspnea is



Figure 1. Bronchogenic carcinoma of the lung. The tumor originated in the main stem bronchus and has extended peripherally along the bronchial divisions. There is severe distal pneumonitis.

a decrease in its cross-sectional area. When this involves a centrally located portion of the tracheobronchial tree or when it is widespread in the distal branches, the physiologic consequence is underventilation of normally perfused alveolocapillary membranes. This imbalance has been emphasized by Motley.

The location of the obstructing lesion is of prime importance. A carcinoma of a main stem bronchus (Fig. 1) is more likely to cause dyspnea than is a distally located adenocarcinoma. The bronchial spasm frequently associated with allergic states, in which thousands of bronchioles and small bronchi are reduced in caliber, is usually associated with dyspnea, whereas the bronchiolar stenosis associated with a granuloma is not.

With central lesions, especially, the appearance of shortness of breath may be delayed until distal disease, a pneumonitis for instance, adds a further physiologic burden to respiration. The central obstruction may reduce the flow of air significantly, but the patient will voluntarily, and often unconsciously, adapt to the underventilation so that dyspnea is unnoticed. An added infection (Fig. 1), which will invariably occur sooner or later, is enough to overcome this perilous balance.

Chronic bronchitis has received increasing attention as a cause of dyspnea. Indeed, Stuart-Harris and Hanley included this symptom along with persistent cough and sputum in a definition of the disease. The fact that chronic bronchitis, thus defined, is an important harbinger of emphysema and cor pulmonale makes it important that the disease be recognized and treated early in its course.

Mucoviscidosis, recognized as a generalized disease of glandular epithelium, has long been known to have profound effects on the lungs of affected infants. More recently, however, adult forms of the disease have been recognized and implicated in the pathogenesis of chronic bronchitis and emphysema.⁵ In the infantile form the elaboration of an abnormal mucus causes obstruction of smaller bronchi with peribronchial infection and resultant fibrosis. Concerning the adult forme fruste of this disease it is postulated that the bronchial lesion develops more slowly but in substantially the same manner.

At the terminal end of the ventilatory system stands emphysema. Despite well over a hundred years of study, no completely satisfactory explanation of the disease either in its morphologic or pathogenetic aspects has appeared. Most hypotheses of the pathogenesis of emphysema, however, invoke the terminal bronchi or the bronchioles as the initial site of damage. This is followed by dilatation of the alveolar spaces and thinning of their septa. These represent the only distinguishing pathologic features of the disease (Fig. 2).

Depending on the point of view, the alveoli may be considered as spaces, and therefore part of the ventilatory system, or as a membranous structure, in which case they form the diffusing portion of the lung. Both viewpoints are correct, and it is difficult, therefore, to assign ventilatory or diffusing functions to disease processes in the alveoli.

Pulmonary edema is an example. Because of transudation of fluid from the alveolar capillaries into the alveolar space (Fig. 3), the gases



Figure 2. Emphysema. The alveolar spaces are widely dilated and the septa thinned. The respiratory bronchioles are also markedly distorted (hematoxylin and eosin; $\times 65$).

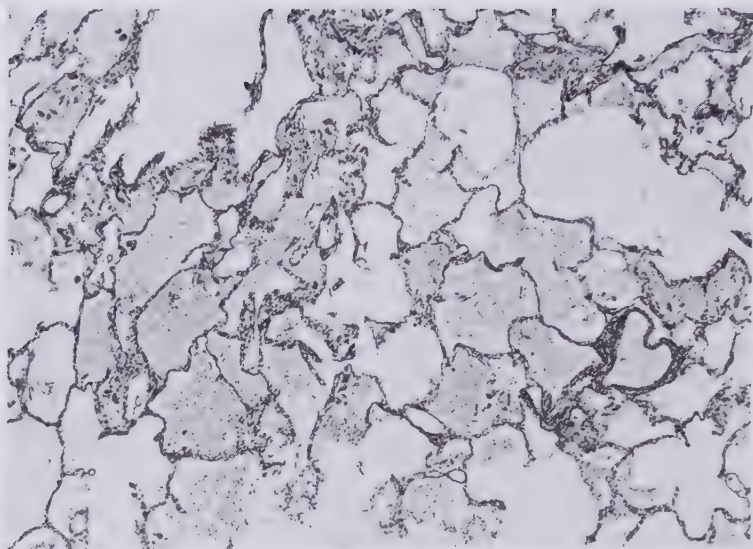


Figure 3. Pulmonary edema. The alveolar spaces contain fluid and the capillaries of the alveolocapillary membrane are distended (hematoxylin and eosin; $\times 30$).

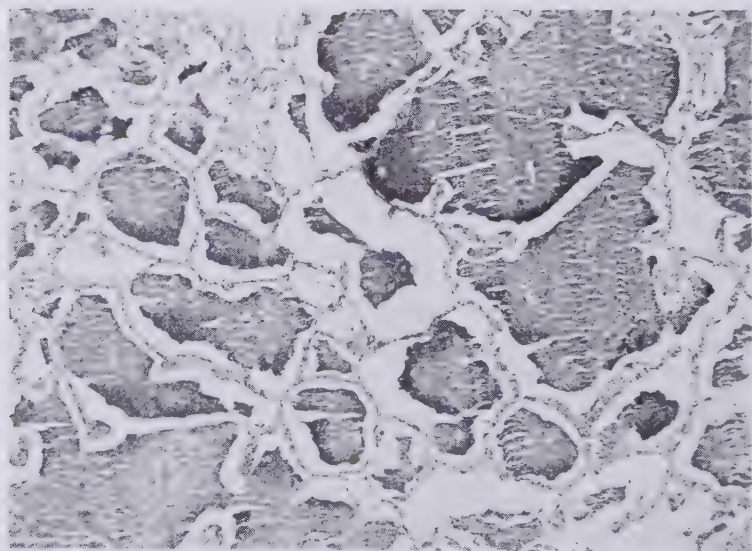


Figure 4. Alveolar proteinosis. The alveolar spaces are filled with a dense, periodic acid-Schiff positive, lipid rich, gel-like material (periodic acid-Schiff stain; $\times 90$).

passing along the conduction system cannot gain access to the alveolocapillary membrane. From a functional standpoint both ventilation and diffusion are impaired.

A similar process is seen in pulmonary alveolar proteinosis. This relatively new disease, first described in 1958 by Rosen and associates, is characterized pathologically by the presence of large amounts of dense, almost gelatinous material with a high lipid content in the alveolar spaces (Fig. 4). The evidence available is consistent with the notion that this material is elaborated by the epithelial cells of the alveolocapillary membrane.

THE DIFFUSION SYSTEM

As Spain has pointed out, the primary function of the lung is the exchange of oxygen and carbon dioxide. The operative word here is exchange. Functionally, this consists of the passage of oxygen from the alveolar space into the capillary blood and the flow of carbon dioxide in the opposite direction. This occurs through the alveolocapillary membrane. Diseases of this structure, therefore, can be expected to have immediate and often profound effects on pulmonary function. Dyspnea, among other signs and symptoms, usually results.

The alveolocapillary membrane (Fig. 5), which forms the wall of the alveoli, is simple in structure. It consists of a lining of epithelial cells which form a continuous sheet over the alveolar surface. Beneath these cells is a basement membrane which often merges and becomes inseparable from a similar structure surrounding the capillaries. Any disease process which interposes material between the capillaries and the lining cells will

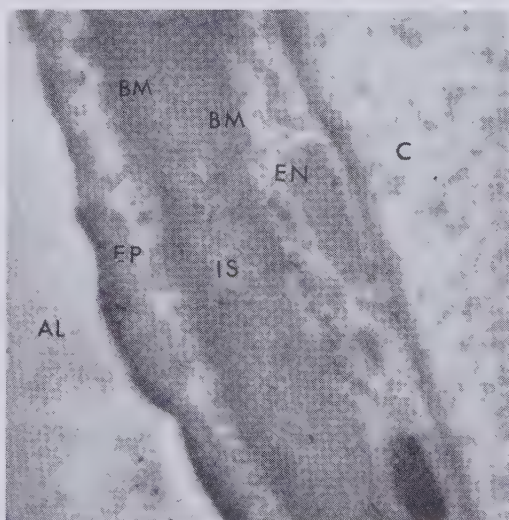


Figure 5. Alveolocapillary membrane. The epithelial cell (EP) lines the alveolar space (AL) and the endothelial cell (EN) lines the capillary (C). Each of these types of cells has a basement membrane (BM) and a variable intervening space (IS). (Electron microscopic view; $\times 35,000$.)

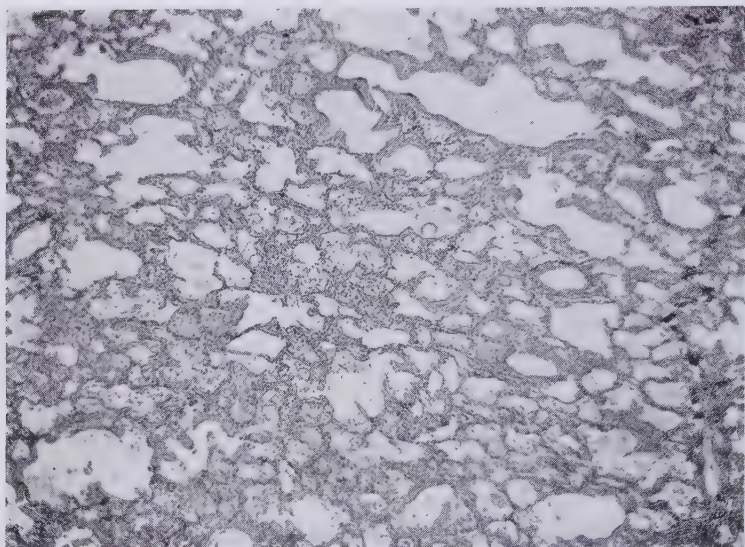


Figure 6. The Hamman-Rich lung. The alveolar septa are increased in thickness due to the presence of fibrous tissue, edema and inflammatory cells (hematoxylin and eosin; $\times 20$).

retard the passage of oxygen and carbon dioxide. This material may be collagen, as in chronic inflammatory diseases, or edema fluid as occurs in viral pneumonitis. Since carbon dioxide is 21 times as diffusible as is oxygen,⁶ an increase in the thickness and a change in the composition of this membrane have the greatest effect on the diffusion of oxygen. This is the basis of the alveolocapillary block syndrome in which the oxygen content of the blood is decreased, but the carbon-dioxide content is generally within normal limits.¹

Besides the interposition of space-occupying material within the alveolocapillary membrane with resultant diffusion impedance, the pathologic process may proceed to the obliteration of the capillaries. This has the effect of shunting pulmonary arterial blood away from ventilated alveoli, the reverse of the situation in obstructive lesions in the ventilatory system.

Several diseases lead to the development of diffuse interstitial fibrosis of the lungs. Among these are sarcoidosis, scleroderma, radiation pneumonitis, berylliosis, rheumatoid disease of the lungs, and the Hamman-Rich syndrome. The end stage of these diseases is similar—diffuse fibrosis of alveolar walls extending to involve the terminal bronchi, obliteration of capillary channels, and hyperplastic changes in the epithelial cells lining the alveoli. Because of this common terminal involvement it is often impossible to define the disease process which was responsible for it.

The Hamman-Rich lung (Fig. 6), also known as chronic diffuse interstitial fibrosis of the lung, has received increasing attention in recent years. Its cause is unknown although infection, hypersensitivity, and a relation

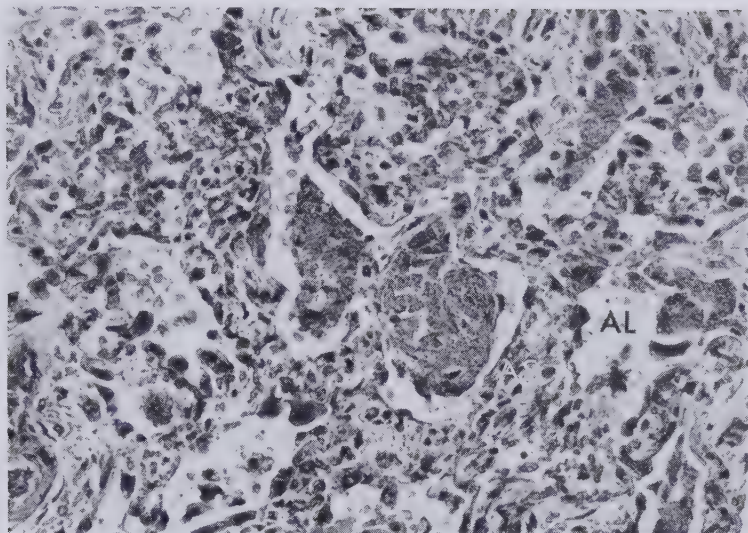


Figure 7. Radiation pneumonitis and fibrosis. The alveolar septa (AS) are thickened by fibrous tissue. The alveolar spaces (AL) contain fibrin, red cells, and macrophages (hematoxylin and eosin; $\times 200$).

to the collagen diseases have been considered.¹² Certain clinical features as well as the pathologic changes make it increasingly difficult to distinguish the Hamman-Rich lung from the lung seen in scleroderma (diffuse systemic sclerosis) and in rheumatoid arthritis.

Although pulmonary sarcoidosis regresses spontaneously⁴ in many cases, diffuse pulmonary fibrosis develops in a significant number. The diagnosis is made from the finding of associated lesions in the lung, liver, and lymph nodes as well as the clinical data.

In addition to the effect on gaseous diffusion, interstitial fibrosis also can seriously impair ventilation. This is due to loss in the elasticity of the lungs by destruction of elastic tissue and the splinting effect of the non-elastic collagen. An example of this is radiation fibrosis (Fig. 7). Although dyspnea is a common feature of this disease, usually the oxygen saturation of the blood remains normal both at rest and during exercise.³ A similar, but less marked, effect on ventilation is often seen in the Hamman-Rich lung.¹

THE PERFUSION SYSTEM

Pulmonary function is just as dependent on adequate perfusion of the alveolar capillaries as it is on adequate ventilation of the alveolar spaces. Not only must the perfusion be adequate in terms of volume, but the blood flow has to be distributed more or less evenly throughout the capillary system.

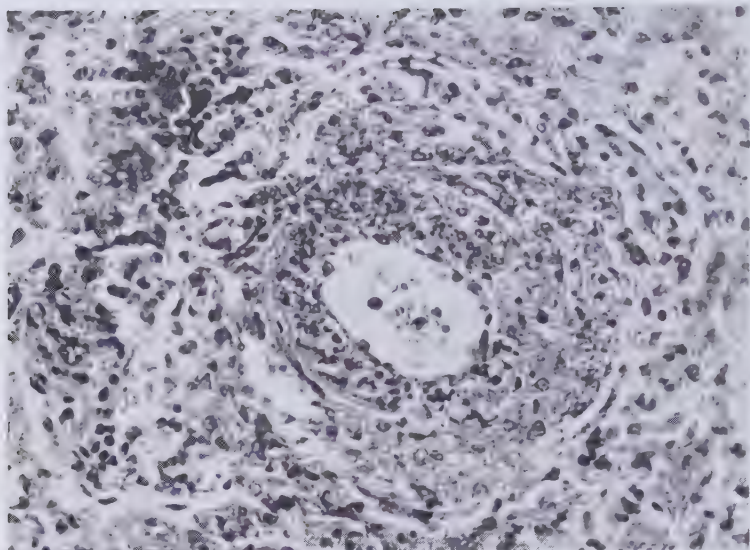


Figure 8. Polyarteritis nodosa. The wall of the artery is infiltrated by inflammatory cells with narrowing of the lumen (hematoxylin and eosin; $\times 310$).

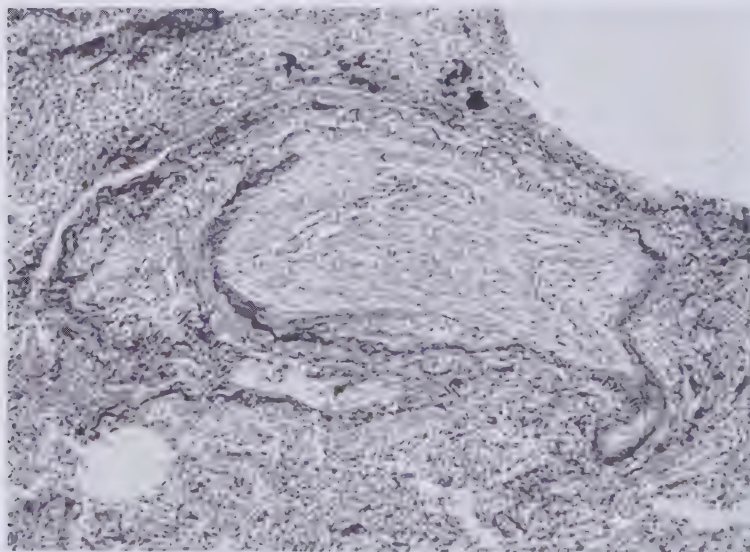


Figure 9. Healed polyarteritis nodosa. Nearly complete occlusion by proliferated intima and organizing thrombus. Only the proximal portion of the smaller branch is involved (elastic tissue-van Gieson; $\times 140$).

Diseases that interfere with the perfusion of the alveolar capillaries do so by decreasing the flow of blood through them or by altering the distribution of the flow. Examples of the causative lesions are pulmonary emboli, diffuse pulmonary vascular disease as in polyarteritis nodosum, scleroderma, and allergic vasculitis, multiple arteriovenous fistulae, and mitral stenosis.

Although the acute effects of pulmonary embolization are well known, the fact that dyspnea and chronic respiratory failure can develop from this is less well appreciated. This clinical picture will become apparent only if a significant portion of the lung is infarcted and, of course, if the patient survives. Recurrent pulmonary emboli may finally so compromise the pulmonary-arterial bed that impaired perfusion, pulmonary hypertension and cor pulmonale result. Dyspnea is a prominent symptom in these patients. The basis of the chronic respiratory failure is underperfusion as well as the eventual fibrosis of the pulmonary parenchyma. The role of the bronchial arteries in modifying or preventing these changes is well known in the experimental animal but has not been satisfactorily defined in the human.

The vasculitis associated with polyarteritis nodosum (Figs. 8 and 9) may involve the lungs with profound effects on perfusion. Frequently, however, survival is short and does not permit diffuse changes and elevated pressure to occur in the pulmonary artery. Because many patients with pulmonary vascular involvement have a history of hypersensitivity, it is

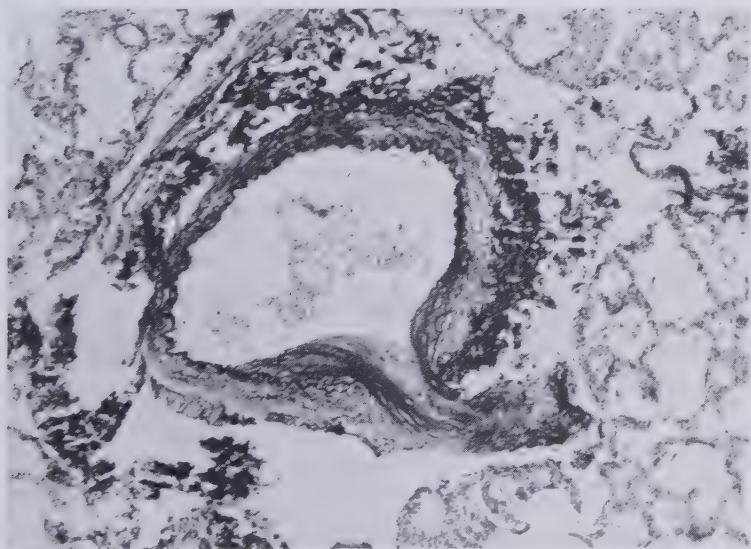


Figure 10. A muscular artery associated with a large ventricular septal defect. The larger vessel is normal but the smaller branch is occluded by the proliferated intima (elastic tissue-van Gieson; $\times 75$).

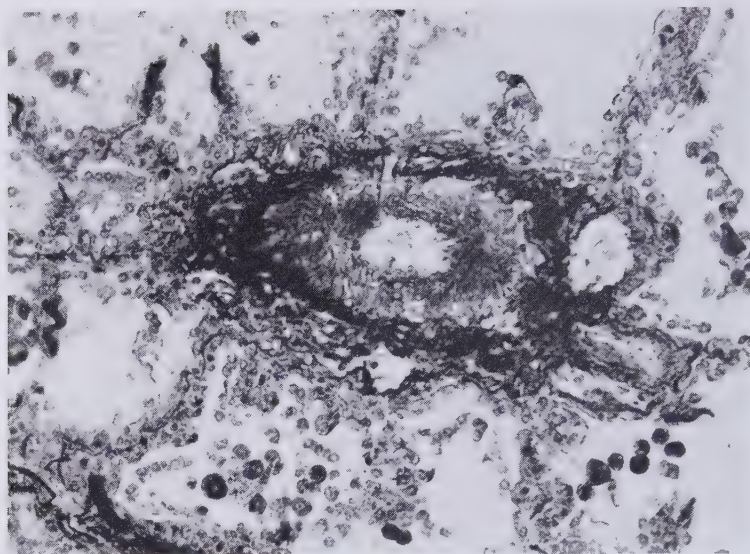


Figure 11. A pulmonary arteriole in chronic congestive heart failure due to mitral stenosis. The media is considerably thickened and the lumen is reduced in caliber (elastic tissue-van Gieson; $\times 200$).

often difficult to distinguish the lesions of polyarteritis nodosum from those of allergic vasculitis.

Cardiac disease, with associated pulmonary hemodynamic abnormalities, may result in severe obliterative lesions in the smaller branches of the pulmonary artery. At least two mechanisms appear to be operative in causing these vascular changes. One is the occurrence and organization of thrombi; the other is long continued elevation of pressure in the pulmonary artery. These vascular lesions may be associated with an increased flow of blood through the pulmonary artery as occurs in left-to-right shunts within the heart. Examples of such lesions are ventricular septal defects, transposition of the great vessels, atrial septal defects, and occasionally, patent ductus arteriosus (Fig. 10).

Chronic heart failure due to any cause is frequently associated with dyspnea and with distinct changes in the pulmonary capillaries and alveolar septa (Fig. 11). This has the functional effect of reducing the compliance of the lung, thereby adding a ventilatory restriction to a reduction in perfusion.

SUMMARY

The pathologic changes in the lung associated with dyspnea are numerous and complex. A few of them have been discussed and illustrated. The lesions have been grouped into those affecting primarily the ventila-

tion, diffusion, or perfusion systems of the lung. Usually, however, such precise morphologic-functional localization is temporary in a given disease with later multistructural and multifunctional involvement.

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Bronchial Asthma—The Acute Attack

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Notwithstanding the accumulation of knowledge concerning the causes of asthma and the many preparations which have been advocated for its treatment, the care of the patient beset acutely with this disease continues to be a challenge. This discussion will relate to the management of status asthmaticus—a situation in which asthma has become so severe, disabling, and refractory to treatment practicable and usually effective in the home that hospitalization is desirable, if not imperative.

THE MANAGEMENT OF STATUS ASTHMATICUS

To relieve the distress there are several courses of therapeutic action, each of which, if indicated in any given case, should be implemented as soon as possible after the patient has been admitted to the hospital.

1. Control of the Environment

The first consideration in management is the elimination of the patient's contact with allergens that may have a major influence in causing his asthma, with smoke, dust and strong odors that may act as bronchial irritants, and with relatives, other patients, and noise that could prevent him from securing rest essential to recovery. He must not smoke either tobacco or asthma cigarettes.

The therapy begins with placing the patient in a specially prepared private room. Ideally it should be devoid of drafts, drapes, flowers, rugs, and the other things mentioned above. Dustproof covers should be on the mattress, and the pillows should be of non-allergenic material like Dacron or encased in plastic covers. The air in the room should be filtered (by a unit fitted into the window or installed at the time of construction of the hospital) to exclude pollen and dust. And finally, if the patient gives a conclusive story of sensitivity to any food or drug, special care must be exercised to be sure that he does not receive it inadvertently.

If the asthma abates dramatically in the first 24 to 48 hours after these environmental controls have been instituted, extrinsic factors probably have been important in causing it. Conversely, if the asthma fails to improve rapidly under such circumstances it is more likely that intrinsic factors are chiefly or substantially responsible for it.

2. Measures to Ensure Rest

Relief of the asthmatic paroxysm by any means cannot be expected until the patient is both mentally and physically at ease. Anxiety is a prime factor in aggravating the severity of status asthmaticus. This, plus loss of sleep, mounting fears, and the tiring effect of repeated episodes of breathlessness lead to a state of utter physical and emotional exhaustion.

The reassuring manner and confident attitude of the physician have important beneficial effect in this situation. Let nothing ever be said in the presence of the patient by either physician or nurse which could lead the patient to believe that his condition is out of the ordinary in any way or that the outcome will be anything but favorable.

We believe that special duty nurses, not only by their constant presence in the room but also by their added attention to his needs and personal administration of prescribed medicaments, help the distraught, agitated asthmatic to calm down and to secure the rest he needs.

The intelligent use of sedatives is also important in this regard, but one must bear in mind always that asthmatic patients as a group tolerate them poorly. Preparations such as chloral hydrate, paraldehyde, and phenobarbital are reliable; and rarely have allergic reactions to these been observed. Chlordiazepoxide (Librium) also may be helpful and certain antihistamines because of their sedative effect may be useful at bedtime. In our opinion, drugs such as morphine, codeine, meperidine (Demerol), and dihydromorphinone (Dilaudid) are to be avoided strictly, some because of their depressant action on the respiratory center and all because of their habit-forming properties.

Finally, it should be pointed out that when severe asthma has been controlled by any or all of the several measures to be considered in this discussion, the patient will relax and secure easily the mental and physical rest that is essential.

3. Measures to Aid in Liquefying Sputum

Such measures are important and may be lifesaving. In many persons who have died in status asthmaticus the terminal bronchi have been found plugged with casts of mucus which they were unable to raise. Control of bronchospasm, to be discussed later, cannot in itself afford the patient much relief unless such blockage of the bronchi can be obviated.

Adequate hydration is one way to combat this problem of thick, tenacious sputum. Intravenous administration of 2 to 3 liters of 5 per cent glucose during each of the first few days of the patient's hospitalization

may be warranted—especially if the weather is warm or if he is not taking fluids well by mouth—and it should be sufficient. One must be careful not to give too much parenteral fluid to an individual whose asthma is complicated by borderline cardiac decompensation or early cor pulmonale with severe emphysema. When the patient becomes able to drink 10 to 14 glasses of liquid daily, intravenous administration of fluids as a hydrating measure may be discontinued.

Expectorants should be accounted only an adjuvant to hydration, since their thinning effect on sputum is negligible until the body fluids are restored. Effective preparations of this kind are sodium and potassium iodide, employed usually in a total daily dose of 0.65 to 1.0 gm. Intolerance, if it occurs, is manifested commonly by pain and swelling of the salivary glands 24 to 48 hours after the medication is started, or as an ioderma that may become apparent after four to seven days of administration. In cases of clinical sensitivity to iodides, ammonium chloride or Robitussin (guaiacolate, prophenpyridamine, codeine) may be substituted expectorants, although their effectiveness in this regard is less.

It has been suggested that highly purified proteolytic enzymes and certain detergent solutions be given by aerosolization for some diseases like asthma in which thick, viscid sputum is a problem; but our limited experience with them in asthmatics has been that they are irritating and provoke coughing, and are not helpful.

4. Control and Elimination, If Possible, of Bronchial Infection

If the patient is febrile on admission, or if his sputum is purulent, then subacute bronchitis may be presumed to be a complicating factor and treatment of it is important in the relief of the asthma. General cultures of the sputum for pathogens may or may not show any.

If administration of a broadly effective antibiotic is continued for seven to ten days, ordinarily the sputum gradually becomes clear, colorless, and mucoid and decreases in volume—sometimes disappearing completely. In most instances the fever subsides coincidentally and the asthma improves consistently with these changes.

The antibiotic used most frequently is erythromycin, but in some cases a combination is required before improvement is noted. Recently a patient was encountered in whom no clinical benefit or change in the character of the sputum was observed until streptomycin and tetracycline (Achromycin) were added to his program. Improvement thereafter was rapid and remarkable: at the time of dismissal he had noted no sputum for three days and his lungs were clear. Triamcinolone also was given him, but its role in the treatment of status asthmaticus will be discussed later.

5. Control of Cough

The attainment of this important objective is expedited by elimination of bronchial infection; and relief of bronchospasm (to be discussed pres-

ently) is impossible without control of cough, since coughing provokes and perpetuates bronchospasm.

As pointed out earlier, elimination of cough is quite dependent on environmental control—namely avoidance of inhalation of respiratory irritants of any type. Also it is related closely to elimination of infections in the bronchi. Many asthmatics, however, develop a habit of overcoughing which itself can be exhausting and debilitating.

The physician should keep encouraging the asthmatic to try earnestly to suppress his tendency to cough. Much can be accomplished by this voluntary effort. Since swallowing inhibits coughing, the patient may get additional help by keeping some hard candy in his mouth. Finally, inhalations of air humidified by steam may mitigate bronchial irritation and thus allay the inclination of some asthmatics to cough.

6. Prevention or Elimination of Anoxemia

Anoxemia may develop consequent to the combination of bronchoconstriction with excessive secretion of mucus by the bronchial mucosa and edematous swelling of this mucosa. It can be prevented or eliminated by control of bronchospasm and inhalation of oxygen.

Of the bronchodilators, aminophylline (a xanthine derivative) is one of the most effective when administered either intravenously in a dose of 0.25 gm. or rectally as a suppository or retention enema in a dose of 0.5 gm. The intravenous dose suggested may be given two to three times in 24 hours with 5 per cent glucose. When the acute phase of the asthma has passed, aminophylline may be given orally, often in combination with an ephedrine derivative and phenobarbital; but with this route of administration its therapeutic efficacy is less.

Ephedrine and related substances like phenylpropanolamine (Propadrine) or methoxyphenamine (Orthoxine) are used commonly with aminophylline and a sedative. Ephedrine is supposed to slow the rate of enzymatic destruction of endogenous epinephrine. It may cause cerebral excitation or increase in the symptoms of prostatic obstruction; hence some care must accompany its use in old men. Orthoxine reputedly has less vasospastic action than ephedrine and thus may be used with greater theoretic safety in asthmatic patients with severe hypertension.

In status asthmaticus, epinephrine and its derivatives usually have lost their effectiveness in relieving bronchospasm, at least temporarily; but trial should be made then, and again when the status is controlled. Epinephrine may be taken by inhalation, for which a 1 per cent solution is employed most frequently. It should be used with some caution in the aged. Patients who are to take it by injection should be instructed in self-administration. This will help to obviate the anxiety they may feel during acute attacks while waiting for the doctor to come.

Isoproterenol, which is the isopropyl homolog of epinephrine, is supposed to cause fewer cardiovascular side effects. It is to be taken only by

inhalation, either as an aqueous solution or as a powder (Norisodrine). It is not to be injected. The inhalation by older patients of measured amounts (as Isuprel) at regular intervals over a period of a few days may be fraught with some hazard to the coronary circulation, and we believe that this type of regular use should be avoided.

Although in the past decade it has seemed that fewer patients require it, the inhalation of oxygen either alone or in combination with helium is another important way to combat anoxemia. Perhaps the tremendous effectiveness of steroids in most cases of status asthmaticus is the explanation for the decreasing need to administer oxygen.

There are three effective means for giving oxygen. The first is a nasal catheter. It is the simplest and affords an effective concentration of the gas, though not so high as the other ways. The second is the oxygen tent. This makes possible a concentration which approaches 50 per cent and has the added advantage of providing the patient with an air-conditioned, allergen-free atmosphere. The third is the BLB mask. This provides the only efficient and economical way to administer mixtures of oxygen and helium, and the device also makes possible the administration of 100 per cent oxygen. If helium is to be part of the mixture employed, it is well to advise the patient that his voice will be high pitched during the period that it is given.

Inhalation of oxygen by patients who have severe asthma without significant degrees of emphysema may be continued for 24 to 48 hours or may be used intermittently, depending on how the patient is progressing. Positive-pressure devices such as the Bennett valve or Mine Safety valve have not proved helpful at the Mayo Clinic in the treatment of status asthmaticus.

7. Use of Steroids

The final avenue of action to be considered is the use of steroids. Although the mechanism by which they alleviate asthma is not established, relieve it they do in most instances. Because of their prompt effectiveness when given orally, we find no occasion to use corticotropin, which must be given by injection and which has been antigenic in some individuals, leading to allergic reactions.

We believe it is completely justifiable to give effective doses of steroids to any patient in status asthmaticus who has not responded in 12 to 24 hours to the standard therapeutic measures just discussed, or whose condition on arrival at the hospital is so critical as to allow no time either to try milder measures or to assess contraindications for steroids.

The preparation we prefer at present is triamcinolone. When the decision to employ it has been made, we start with doses of 8 mg. four times daily and continue thus until substantial improvement is noted—in most instances three to five days. The dose may be dropped then to 4 mg. four times daily and continued at this level for another four to six days.

Recovery may be expedited, in critically ill patients, by adding 100 mg. of hydrocortisone (Solu-cortef) to each of two bottles of fluid given intravenously during the first day of the patient's hospitalization.

The exact schedule adopted for tapering off and stopping the administration of triamcinolone is a matter of individual experience and preference. It seems likely that a continuation of the patient's improved state depends more upon avoiding respiratory infections and giving attention to the principles of management presented in this paper than it does on whether the tapering schedule requires two months or four to six months. We have seen tapering completed in two months followed by a symptom-free period of two months or longer, but also recurrences within one month after the start of a tapering schedule planned to continue for several months.

A satisfactory practical plan is to prescribe 2 mg. of triamcinolone four times daily at the time of dismissal and instruct the patient to decrease the total daily dose by 1 mg. at the beginning of each subsequent week. This program eliminates steroid medication in eight weeks. Should status asthmaticus recur, one need not be reluctant to repeat such a course of treatment, if necessary, once or twice in one year.

The undesirable side effects of steroids are well known, but they are not likely to arise from the short, intensive courses described. In deciding to use them—even in the presence of such deterrents as duodenal ulcer, diabetes mellitus, or hypertension—one must weigh the hazards of the asthmatic state against those of the steroids themselves and their possible bad effect on the associated condition.

CONCLUSION

In closing, one may observe that it is not too difficult to outline didactically a program of treatment for status asthmaticus, but in practice all of us encounter cases that tax our therapeutic ingenuity to the limit. In most instances, however, the therapeutic principles set forth here will prove to be effective.

Office Management of Chronic Bronchitis and Emphysema

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In an introduction to a discussion of the management of chronic bronchitis and emphysema,* it seems appropriate to attempt to define the magnitude of the problems created by this disease. Many of us in the practice of medicine are impressed by the increasing number of people seeking medical help for diffuse obstructive lung disease. In support of this impression are mortality statistics showing that deaths reported as due to emphysema increased 158 per cent between 1954 and 1959.⁸ It is likely that this increase is due in part to increased awareness of this disease on behalf of physicians. Even so, there is little question that the number of people suffering from chronic bronchitis and emphysema really is greater than it was.

It is difficult to establish the prevalence of chronic bronchitis and emphysema in the United States. Results of surveys vary considerably, but suggest that from 4.9 to 26.5 per cent of American men over 40 years of age demonstrate evidence of chronic obstructive disease of the airway.² Furthermore, of the workers in the United States granted disability benefits by the Bureau of Old Age and Survivors Insurance in 1960 because of a specific chronic disease, 6.9 per cent had emphysema and an additional 0.4 per cent had bronchitis. This figure exceeds the combined total of people securing disability benefits with respiratory-tract malignancy or tuberculosis.⁸

Hence, the magnitude of the problem is apparent. As physicians, we should not slight the treatment of this chronic disabling disease, as has so often been done in the past, by simply informing the patient that nothing can be done to help him. While this is true to the extent that nothing can be done to reverse most of the anatomic changes in bronchitis and emphysema, a good program of management can protect the patient from some

* In this paper we have made no attempt to distinguish between chronic bronchitis and emphysema, but have used these terms interchangeably.

of the complications, probably delay the progression of the disease, and sometimes improve pulmonary function. It also assures the patient of his physician's interest in his problem and gives him hope.

Our methods for management of chronic bronchitis and emphysema in the ambulatory patient, which have been developed on the basis of our clinical experience, are presented in the following paragraphs. In our experience it has been helpful to have the spouse or some other responsible person in attendance during instruction of the patient.

EVALUATION OF THE PATIENT AND EDUCATION REGARDING HIS DISABILITY AND HIS ACTIVITIES

An appropriate introduction is a simple review of the pathology and pathophysiology of emphysema. Simple sketches depicting narrowed airways with hyperinflated and disrupted alveoli are very useful in helping the patient visualize his problem. The intelligence of the patient dictates to some extent how detailed the discussion becomes, but it is worthwhile to observe how well most patients comprehend this information and relate it to their own experiences.

It must be clearly and emphatically pointed out to the patient early in the course of the discussion that the primary objective of any treatment program is the preservation of existing lung function or at least a slowing of the disease process. While improvement in function may take place as a result of therapy, it cannot be promised. Understanding this, the patient will be less likely to reject the sometimes tedious program of management if he does not experience the hoped-for improvement.

The nature and extent of the patient's physical activities need to be reviewed. He should be encouraged to walk leisurely and avoid excessive dyspnea, something many find difficult to do. At the same time, he should be encouraged to undertake some physical activity such as walking every day. Others accompanying the patient can help by walking slowly.

An evaluation of the patient's job is necessary, for often a change to work requiring less strenuous physical activity or involving less exposure to respiratory irritants is demanded. Here the physician can be of help—for example, by making recommendations to the patient's employer and aiding in obtaining vocational rehabilitation.

The emotional problems in this disease can be considerable. Not uncommonly a patient is discouraged at not being able to work, anxious during periods of acute dyspnea, and afraid of the prospects of complete invalidism. Anxiety itself may increase the dyspnea. In such a situation, a careful explanation of what the problem is, why the dyspnea occurs, how panic compounds the problem, and what the patient can do to help himself can be very reassuring. In some cases the judicious use of mild tranquilizers is helpful.

REDUCTION OF EXPOSURE TO BRONCHIAL IRRITANTS

It is absolutely necessary that the patient stop cigarette smoking if he is to slow the progression of his disease. Although the etiology of bronchitis and emphysema may involve factors other than cigarette smoking, such as community air pollution, constitutional factors, and so on, the physician must be emphatic in his advice to stop smoking. Patients have justified continued smoking by what they have interpreted as ambivalence of their physician regarding the need to discontinue it. If the patient decides to continue smoking, it should be his own decision unfostered by his physician. In our experience, it is useful to explain the evidence linking cigarette smoking to chronic bronchitis and emphysema. The patient should understand that it is extremely rare for a nonsmoker who does not have chronic asthma to develop emphysema, and that the condition can only be expected to worsen as long as he smokes. While a number of preparations are reputed to help overcome the smoking habit, there has not been wide acceptance of any. If the patient absolutely cannot quit smoking, pipe or cigar smoking—although not free from producing bronchial irritation even when the smoker does not inhale—is a reasonable substitute.

Exposure to dusts of various kinds, fumes such as exhaust gases from vehicles or even perfume, humid air, or cold air frequently aggravates dyspnea or causes cough and should be avoided. Since the patient may have been chided already by members of his family for what they consider an unreasonable hypersensitivity to odors, it may be of help to them to understand that this is a common phenomenon. At times dust masks can be used to advantage. During cold weather the patient should try wearing a scarf which he can hold up over his nose and mouth and through which he can breathe to warm the frosty air. As mentioned earlier, it may be necessary for the patient to change employment to avoid respiratory irritants.

The question of the value of a change in climate is frequently asked by the patient and can be difficult to answer. Undoubtedly some patients do better in a warm, dry climate; but it is advisable not to overemphasize this point, for the benefits may not justify the economic loss in moving. It should also be pointed out that few localities have year-round weather ideal for the patient with emphysema. Finally, before a permanent move is made, the locality to which the patient proposes to move should be visited.

CONTROL OF BRONCHIAL SECRETIONS

Excess mucus is present in the tracheobronchial tree of practically all patients with chronic bronchitis and emphysema. Particularly when it is tenacious, it increases the obstruction to air flow. Mucus which has col-

lected in the bronchial tree during the sleeping hours accounts for the increased shortness of breath which these patients commonly experience during the first hour or two after rising. Patients may have difficulty raising these secretions because the marked slowing of air flow during expiration makes their cough ineffective. Therefore measures to reduce the amount and viscosity of mucus in the respiratory tract are very important. Of primary importance is the treatment of any infection (see below). Adequate fluid intake (12 to 15 glasses per day) is helpful. Of the available expectorants, saturated solution of potassium iodide in a dose of 10 to 15 drops three times daily in water or fruit juice is most often used. If gastric irritation ensues, the medication should be taken after meals. It is well to forewarn the patient of the possibility of an iodide reaction.

During the winter months the relative humidity is low in many homes, and respiratory-tract membranes become excessively dry. Humidifiers, in the bedroom at least, are useful in overcoming this. If difficulty with secretions continues after infection has been treated, fluid intake increased, and expectorants given, then heated-mist inhalations deserve a good trial. Several companies make effective heated-mist generators which can be operated by compressed air or electrically driven air compressors. Twenty to thirty minutes of airway humidification by this means twice daily has been very helpful in reducing cough and secretions. Postural drainage also should be tried, though for someone already short of breath the stress involved in carrying out postural drainage can be very fatiguing. Enzymes, such as pancreatic dornase or trypsin, and wetting agents administered by inhalation have been used in efforts to thin bronchial secretions. However, these agents may be irritating to the tracheobronchial tree, and the harm of additional bronchial irritation may outweigh the benefit obtained. Finally, if tracheobronchial secretions are still a significant problem despite all of the described measures, consideration can be given to the establishment of a permanent flap-type tracheal stoma that will enable the patient to aspirate these secretions as necessary.

CONTROL OF RESPIRATORY-TRACT INFECTIONS

The increased susceptibility to respiratory-tract infections which is displayed in many cases of chronic bronchitis and emphysema can be negated to some extent if the patient will try to avoid contact with persons who have respiratory-tract infections, to avoid crowded public gatherings when respiratory-tract infections are most prevalent, and to avoid over-fatigue. Immunization with the Asian flu vaccine is recommended unless there is an allergy to eggs.

Infections of the upper part of the respiratory tract should be met promptly with rest, fluids, aspirin, and the other usual measures. If the lower respiratory tract is involved, antibiotic therapy—preferably tetra-

cycline in a dose of 250 mg. four times daily—should be instituted without delay.

There is evidence that the daily administration of tetracycline will reduce the number and duration of respiratory illnesses in patients with chronic bronchitis.^{4, 7} The cost of this chemoprophylaxis is considerable, however; so we prefer to reserve therapy with tetracycline for the specific infection. The success of such a program is contingent on the early institution of therapy, which means that the patient must be impressed with the need of reporting infections to the physician promptly. In the patient with associated bronchiectasis and a copious amount of chronically purulent sputum, the cyclic administration of tetracycline in a dose of 250 mg. four times daily for five days every three to four weeks has been tried with good results.

Many flare-ups of lower respiratory-tract infections seem to have no specific organism as the cause; at least cultures of sputum grow only the usual bacterial flora. Purulency of sputum therefore is sufficient indication of infection to justify a trial of antibiotic therapy. The frequency with which *Hemophilus influenzae* and pneumococci are found in the sputum of patients with chronic bronchitis varies with the season of the year and the frequency with which bacteriologic examinations of sputum are carried out.⁵ What these organisms have to do with acute flare-ups of infection is not clear. We believe that pneumococci, when found in cultures of sputum, should be eradicated by therapy with penicillin, erythromycin, or tetracycline in the usual doses. Infections with *H. influenza* are more resistant; and tetracycline, 0.5 gm. four times daily for five or six days, or streptomycin, 0.5 gm. intramuscularly twice a day, is advised.

Although mucoid sputum usually does not contain pathogenic bacteria, culture of such sputum is indicated when a patient's condition has worsened without apparent reason, for sometimes a significant infection can be uncovered in this way. Indeed, any patient whose condition has worsened without explanation deserves a trial of antibiotic therapy.

On occasion, cultures of purulent sputum may grow only *Pseudomonas aeruginosa* in significant numbers. Under these circumstances, therapy consisting of polymyxin B given by aerosol or of colistin, 2.5 mg./kg. body weight/day given intramuscularly in two divided doses is worthy of trial. Such therapy should be limited to about a week with observation for evidence of renal toxicity.

BRONCHODILATING DRUGS

Isoproterenol or racemic epinephrine, administered as an aerosol, can have an important part in the medicinal treatment of bronchitis and emphysema. When effective, these medications produce measurable decreases in airway resistance and lessen dyspnea. Instructing the patient in

the proper use of a good nebulizer and checking to see that he continues to use it properly ensure the maximal effect from the medication and the time spent. Best results will be obtained with a nebulizer if on every third or fourth breath the patient exhales almost completely and then, during maximal inspiration, squeezes the bulb flat several times. He should hold the full breath a few seconds and then exhale. This deep breathing overcomes some of the unevenness of ventilation and achieves better distribution of the drug. The average dose is 8 to 10 drops of 1:200 isoproterenol diluted with 4 to 5 drops of distilled water, given at least three times daily. It is important that the first treatment be undertaken immediately upon arising in the morning, when most patients experience their greatest dyspnea. Nebulizing this dose of medicine with the hand-bulb nebulizer will require about 10 minutes. Since hand nebulization can be fatiguing, patients should be familiarized with machine-powered air compressors or with ready-supplied compressed oxygen or air, which can be used to operate their nebulizers with greater ease and possibly greater efficiency. Occasionally, objectionable palpitation or jitteriness ensues after the inhalation of this dose of medicine, in which event the patient should extend the period of inhalation of the drug or reduce the dose. Naturally, the dose must be determined by the patient's response.

Commercially prepared, metered-dose nebulizing units which contain either isoproterenol or racemic epinephrine are excellent for the patient to carry at all times to use in episodes of acute increase of airway obstruction or on whatever occasions the use of the hand-bulb nebulizer is not feasible. In our experience, however, irritation of the mucous membrane has been encountered more frequently when these nebulizing units are used regularly than when the plain isoproterenol is used. With this complication, it is advisable to reduce the dose or discontinue administration altogether for a time.

Oral bronchodilators are definitely effective in many patients and are used to supplement therapy with aerosol bronchodilators. Most of these preparations contain a combination of ephedrine, theophylline or a derivative, and a barbiturate. It is well to inquire whether a patient has symptoms of urinary obstruction, for ephedrine may aggravate these symptoms. In such an instance, or perhaps generally for older men, it is advisable to use only the theophylline. If feasible, the patient should take the oral bronchodilator three times daily one to two hours after using the aerosol bronchodilator.

BREATHING EXERCISES

Although there is debate about the value of breathing exercises in improving the ventilation of patients with bronchitis and emphysema,^{1, 6} we have patients who report an increase of exercise tolerance when they

breathe as instructed. This observation does not help to determine whether the effect of breathing exercises is purely psychological or whether ventilation is improved also. Our opinion, however—based upon the existing knowledge of the mechanics of airway obstruction—is that if a patient can be taught (1) to exhale through pursed lips gradually and as completely as possible without exerting great effort, (2) to inhale rapidly, thus allowing a greater proportion of the respiratory cycle for exhalation, and (3) to contract the abdominal muscles gently during expiration, his alveolar ventilation will improve. This type of breathing is especially helpful when the patient exercises or becomes dyspneic. Undoubtedly, the enthusiasm with which these exercises are prescribed can influence the extent to which the patient masters and uses them.

INTERMITTENT POSITIVE-PRESSURE BREATHING (IPPB)

Considerable difference of opinion also exists regarding the value of intermittent positive-pressure assistance of breathing in the day-to-day management at home of the patient with chronic bronchitis and emphysema. There is no question about its value in the management of patients in respiratory acidosis, and it does provide an excellent means of administering aerosols of various kinds. However, if a patient uses his nebulizer in the previously described manner—and particularly if he uses the nebulizer with an air compressor—he probably gains little more by using an IPPB machine. We frequently have patients try IPPB with bronchodilator aerosols and compare the effects noted with the effects of the same medication by nebulizer alone. An occasional patient, on the basis of such a comparison, may choose to purchase an IPPB machine. The practice of prescribing a period of IPPB once or twice a week is of doubtful value and should be discouraged.

CORTICOSTEROID THERAPY

On occasion the pulmonary function of a patient with bronchitis and emphysema is improved by administration of corticosteroids.³ It is presumed that such a patient has bronchospasm or bronchial mucosal inflammation or edema which is favorably influenced by such therapy. In the great majority of cases, however, no objective improvement in function follows the administration of corticosteroids. The subjective improvement which these patients may experience is not justification for long-term corticosteroid therapy in most instances. A trial of corticosteroid therapy, if given, should be terminated within a month if the desired objective improvement is not experienced. Corticosteroids are often used in acute

respiratory acidosis and may be considered in the terminal phase of this disease, where the risks attending such therapy become acceptable.

MISCELLANEOUS MEASURES

Secondary polycythemia, when it occurs, should be treated by phlebotomy to keep the hematocrit value below 55 per cent. The signs of early right ventricular failure should be sought, and appropriate treatment instituted when they are found.

Patients with chronic bronchitis and emphysema commonly experience digestive disturbances and become short of breath if they attempt to eat a meal of normal size. As a consequence, they restrict their intake and lose weight. Unless weight loss is desirable, they should be encouraged to take small feedings to avoid this distress, and to eat more frequently.

Surgery for diffuse obstructive pulmonary emphysema has few proponents at the present time. The value of surgical stabilization of the lower part of the trachea and main-stem bronchi remains to be established in the further course of experience.

SUMMARY

Chronic bronchitis and emphysema constitute a disease without cure. As in any other chronic disease, helping the patient to understand and live with his handicap is the cornerstone of management. A sympathetic and interested physician, even though he cannot cure his patient, can do much to help him. A good program of management will protect the patient against some of the complications, possibly slow the progression of the disease, and sometimes actually improve pulmonary function.

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Principles in the Selection and Use of Mechanical Ventilators and Assisters

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The use of mechanical devices to control, assist, or modify pulmonary ventilation appears to be increasing. Many manufacturers recently have marketed "new" or "improved" ventilators, with features purported to make them safer, more reliable, more versatile, more economical, simpler to operate, and even "more physiologic" than their competitors or predecessors. That these mechanisms are finding widespread use in an ever-increasing variety of situations both within and outside the hospital is evidenced by the expanding appearance in recent medical literature of articles and books concerning their application.

BASIC FUNCTIONING AND CLINICAL DISTINCTIONS

Regardless of the mechanisms involved, all ventilators are designed either to produce or to modify the cyclic expansion of the lungs. According to the design of the equipment and intent of the operator, this is done with dry or humidified air, oxygen, a mixture of the two, an anesthetic mixture, or any of these carrying various medicaments in suspension. The necessary power for this function is derived from compressed gas (which may or may not be that delivered to the lungs), from the hand or foot of the operator, from an electric motor, or from various combinations.

Candidates for respirator therapy may be categorized as having either control or mechanical respiratory insufficiency (Table 1). Control insufficiency is a broad category including central nervous system depression from drugs, trauma, or disease, derangements of the efferent nervous pathways from a variety of causes, and abnormalities of respiratory muscle resulting in subnormal response to efferent impulses. Mechanical insufficiency, which occurs in many more cases, includes all those caused by any degree of airway obstruction, by loss of compliance of the chest wall, or by loss of compliance of the lung.

Table 1. *Bases of Respiratory Insufficiency*

DEFECTS OF CONTROL	DEFECTS OF MECHANISM
1. Damage to central nervous system Trauma Tumor Circulatory derangement Hypoxia	1. Airway Bronchopleural fistula Asthma and pulmonary edema Bronchiectasis Tracheobronchitis Laryngeal, tracheal, or bronchial tumors
2. Effects of drugs and poisons Overdose of anesthetics or other depressants Organic phosphate poisoning Poisoning by strychnine, etc. Bacteremia Anaphylaxis	2. Chest wall Crushed chest Pneumothorax, hemothorax Pleural effusion Congenital or acquired deformity Ascites
3. Neuromuscular deficiencies Poliomyelitis and other neuropathies Myasthenia Myopathies	3. Lungs Emphysema Pneumonia Fibrosis Circulatory defect

Patients having control insufficiency require automatic cycling as well as pressure change to ensure *ventilation* by respirators. Those having mechanical respiratory insufficiency, however, are usually able to establish a satisfactory equilibrium through use of their intact control mechanism to start the pressure cycle of the respirator by their own inspiration—the mode called *assisted respiration*.

TYPES OF EQUIPMENT

Various ventilators have been adapted or designed for use with anesthesia machines so that the benefits of mechanical ventilation can be provided throughout the operative period. Although the various functional elements are similar to those of standard apparatus, most of these machines work by alternate pressurization and venting of a closed chamber which contains the rebreathing bag or bellows of the anesthesia circuit.⁷ Therefore they are not suitable for convenient use outside the operating room.

Controlled-Respiration Type

The simplest of the mechanical ventilators is a bag-and-mask or a bag-and-bellows arrangement such as the Ambu or the Kreiselman Bellows. A system of one-way valves in each provides a non-rebreathing circuit, and provision is made for the addition of oxygen to the bellows intake. The operating power is supplied by the therapist. These are excellent

emergency ventilators, small and inexpensive enough to be readily available in ambulance and ward, and efficient for short-term application. It is a significant safety factor that the operator must stay with the patient, precluding many of the complications seen with automatic apparatus. Standard fittings are available to adapt this equipment easily for use with endotracheal tubes or tracheotomy cannulas.

Tank or chamber respirators designed to apply a negative pressure to the thoracic wall have had wide application in the management of chronic and subacute respiratory insufficiency. The "iron lung" has become familiar to everyone through its widespread use in cases of poliomyelitis over a number of years. The large size and weight, the expense, the difficulty in accomplishing the necessary care of patients so confined, and the availability of smaller and more economical demand units have resulted in a decrease in the application of this type of apparatus. The cuirass respirator was designed to operate on the same principle by use of a smaller-sized chamber to enclose only the chest and abdomen. Some models with portable power supplies have seen application in transporting respirator patients, in ventilating anesthetized or curarized patients during endoscopic procedures, and in weaning respirator patients from their full-time dependence on other mechanical breathing devices.

Rocking-bed respirators have been used in mechanically supported ventilation, and they too are valuable in the difficult period while patients are reducing their dependence on respirators of other types.

All of the mechanisms described above function at a rate adjusted by the therapist rather than the patient. The rate so selected may provide proper ventilation, but is more likely to be too rapid or too slow; or if the patient has any respiratory effort of his own, he may not be able to coordinate it with that of the machine.¹

Assisted-Respiration Type

The successful design of a "demand" apparatus, which begins its cycle in response to the patient's attempt to inspire, has caused a great swing away from the types described earlier to the smaller, less expensive, and more portable kinds which can function as either automatic-cycling or assister respirators.¹⁰

A mechanical device for assisting ventilation must provide: (1) a switching mechanism which will respond to a small drop in airway pressure by delivering a flow of gas; (2) a means of stopping the gas flow when an adjustable, predetermined pressure is reached in the patient system; (3) a means of sealing the airway during the delivery period; (4) a device for venting the airway at the end of the inspiratory period without increasing dead space or expiratory pressure; and (5) a means of humidifying inspiratory gas which will not increase expiratory pressure. Such a device can control ventilation in suitable patients by the addition of an adjustable timing mechanism.⁶

Theoretically, assisted respiration as well as controlled would be possible with use of the subatmospheric pressure tank type of apparatus rather than the type which applies intermittent positive pressure (IPP) to the airway. The necessary mechanism, however, is complex, cumbersome, and expensive.

When any IPP device is used as an assister, a sealed airway is necessary. Devices to overcome major airway leaks have been requested by poorly informed physicians, and some manufacturers have advertised this capability in their equipment. Adequate precision in control of ventilation is not possible with such apparatus; and if there is no appreciable sign or signal of an alteration in function, the equipment can be dangerous.

SELECTING AND PLANNING FOR EQUIPMENT

Different makes of respirators vary considerably in their mechanisms, but we do not intend to dwell on their particular merits and shortcomings. When considering the purchase and use of mechanical ventilators, many factors are to be evaluated. In addition to the cost, size, application, and function one should investigate such things as the difficulty of maintenance, the availability of service and replacement parts, and the ease of cleaning or sterilizing the components. Since there will never be a foolproof apparatus, one must also consider the personnel who will oversee its function in addition to those who will start the therapy. The best equipment for a given application is not necessarily the one with the greatest versatility, since the greater complexity of this type of respirator presumes an exceedingly well-trained and skillful therapist, highly skilled and experienced nursing personnel, an active and enthusiastic respirator service, and an informed staff of physicians.

In larger institutions there is a commendable trend toward centralizing the respirator service. Having the equivalent of an intensive care unit where candidates for respirator therapy may be transferred assures the patient of the safest program, administered by the most experienced personnel and supervised by interested and qualified specialists. A number of such units have been established at larger centers throughout the world, and their value is now beyond question.

PRIMARY CONCERNS IN MECHANICAL VENTILATION

Airway

Regardless of the type of respiratory insufficiency, and no matter which type of apparatus is selected for its treatment, the common denominator of success is a patent airway. Obstruction of the airway by mucus,

anatomic structures, blood, or foreign bodies is especially unfortunate in automatic or time-cycled ventilators because the cyclical function of the machine may not change enough to alert the nursing staff. With chamber ventilators, pulmonary edema is prompt to develop; in IPP respirators, serious hypercapnia and hypoxia result. With a completely helpless patient, the onset of partial obstruction may be insidious enough to escape detection during the first few periodic checks. Therapists should be encouraged to be suspicious always in caring for these patients, and should be intolerant of noisy respiration, since noise means obstruction.

For short periods, a face mask can be used in many instances with IPP breathing. In the flaccid patient, it is necessary most often to use nasopharyngeal or oropharyngeal airway props, in addition to extending the chin and holding the jaw forward. Oropharyngeal airways are not well tolerated by conscious patients, and may produce laryngospasm or vomiting if unwisely used when reflex pathways are intact. Face mask straps help to hold the mask in place, particularly during short-term aerosol therapy with the IPP apparatus, but should never be used alone in the unconscious or helpless patient.

When, because of anatomy, duration of therapy, or continued soiling of the upper airway, a mask provides an inadequate seal, an intratracheal tube often is placed through either the nose or the mouth. After it has been in place for a fraction of an hour, the presence of such a tube is fairly well tolerated by all but the most alert patient; but the introduction of the tube requires flaccidity of the patient, topical anesthesia of the pharynx and larynx, or some other type of interruption of the reflex pathways. If the tube is to be connected to an intermittent positive pressure apparatus, it must fit well enough to resist leakage of inflating air between tube and tracheal wall; otherwise, ventilation will be inadequate. Whenever possible, a cuffed tube is desirable.

Tracheotomy is the best measure for establishing long-term care of the patient receiving IPP respiratory support, and is widely used to facilitate management of secretions in patients in tank or chest respirators.⁸ Cuffed tracheotomy tubes can effect a good seal in adults; but in infants such is not the case, and the problems with tracheotomy and most other facets of ventilatory support seem to increase exponentially as patient size diminishes.

Tracheotomy itself introduces other difficulties. In addition to the surgical considerations of the procedure—such as hemorrhage, pneumothorax, and infection—the presence of the tracheotomy tube makes it impossible for the patient to cough effectively, and swallowing becomes painful and difficult for many during the first week or two. It should not, therefore, be considered as a panacea. If only short-term therapy is to be necessary, an intratracheal tube usually will suffice. We have kept one in place for 72 hours, changing it twice a day, without difficulty.

Ventilation

Since pulmonary function is the exchange of gases between the atmosphere and the blood through the alveoli of the lungs, ventilatory adequacy can be judged by measuring arterial gas concentrations. The central respiratory control mechanism responds to arterial gas concentrations, and through this feedback mechanism regulates the respiratory muscles to maintain respiratory homeostasis. When such adjustment is inadequate the patient may or may not be aware of it and may or may not experience dyspnea. When the nervous system is intact and the respiratory muscles are capable of some activity, this control system should be used to regulate the *rate* of ventilator assisted respiration. By increasing airway pressure and thus tidal volume until the respiratory rate slows, one establishes the effectiveness of the control circuit. After this the central control usually can adjust ventilation satisfactorily by increasing or decreasing the rate of demand cycling of the apparatus at this setting.

Many devices now provide for demand cycling to override a preset slower rate for controlled respirations. This affords continued (though possibly insufficient) ventilation for the patient being assisted by the ventilator who suddenly stops all voluntary effort. It is vital that the change in mode be noted promptly by nursing personnel.

When the central mechanism is not intact, another means of control of ventilation is required. Subjective reports or signals from conscious patients may be helpful, since in many instances patients may feel dyspnea with underventilation, or may be uncomfortable from overventilation. Concentrations of gas in the blood may also be measured from time to time,* but the ideal control available from continuous monitoring, as is effected by the central nervous system, has no man-made equivalent as yet. By judicious interpretation of the results of these measurements, with consideration for body temperature, size, and activity, one may follow grossly the adequacy of carbon-dioxide elimination and the efficiency of the therapy.

Since gravitational effects inevitably cause collapse of dependent portions of the lung, full inflation of the lungs should be accomplished at regular intervals. This can be provided by increasing inspiratory pressure 10 to 20 cm. of water above the set pressure for two or three breaths. When very high pressures are being used (in mechanical restrictive disorders), this is not so necessary.

Treatment with bronchodilators via the airway is generally accepted as effective therapy for emphysema as well as asthma. In emphysema, improvement of ventilation is best obtained by increasing the tidal volume and decreasing the rate, maintaining passive expiration. One must avoid

* Tidal gas sampling of carbon-dioxide concentration, though usually adequate for control, can give what amounts to negative indications and be misleading. For example, tidal carbon dioxide can decrease during the onset of carbon-dioxide retention in the blood thus falsely suggesting a need for decrease in ventilation.

slowing the respiratory rate by mere decrease of inspiratory flow, however, since that is not always accompanied by an increase in tidal volume. Usually it is best to increase airway pressure to a point short of discomfort, thus increasing tidal volume, without restriction of inspiratory flow. This produces better ventilation with a slower rate, because of an increase in the passive expiratory period.

We believe that disagreements concerning methods of assisting ventilation stem largely from differences in emphasis and failure to agree on definitions. IPP therapy is here to stay. It still is used too rarely as a preventive measure, too often only as a last resort.

Humidity

Whenever the nasal structures are bypassed, as by intratracheal intubation or tracheotomy, it becomes essential that the gas delivered to the airway be saturated with water vapor. Each 10 liters of gas saturated at body temperature contains 0.434 ml. of water. A normal adult may evaporate up to 1500 ml. of water per 24 hours in humidifying the inspired air as it passes through the upper airway structures. Bypassing this mechanism results in rapid drying of the lower respiratory mucosa and soon encourages a refractory tracheobronchitis. All IPP machines should be equipped with a humidifier able to saturate the gas fully at body temperature.

Tracheotomized patients should be provided with humidified air or gas mixture throughout the period of therapy. The problems involved in providing this amount of humidity are not so simple as one might think. Steam generators tend to produce either too much heat or too little vapor. Nebulizers and atomizers must produce droplet or particulate water of a size that will be carried into the lungs to provide vapor as the temperature rises. The most effective ones seem to be combination heater-nebulizers. If flow is continuous, one must be sure that the humidifier does not cause a positive pressure during the expiratory phase of the respiratory cycle.

SECONDARY PROBLEMS

Circulatory Effects

Increased airway pressure inflating the lungs increases intrathoracic (extrapulmonary) pressure; whereas normal inspiration is brought about by a reduction in this pressure. Thus the mean systemic vein-to-right-heart pressure gradient is reduced and venous return will decrease. The normal circulatory system can compensate for this; but when blood volume is reduced or the circulatory system is embarrassed by disease or trauma, positive pressure may cause a fall in arterial pressure. Blood replacement, digitalization, or other supportive measures may be necessary when positive

pressure is essential to maintain pulmonary ventilation. It should be emphasized that the same mechanism also reduces venous return when negative pressure is applied around the body.

Fluid Balance

While a patient is receiving long-term respiratory control or assistance, carbon-dioxide homeostasis is largely a function of the mechanical apparatus. Hence metabolic adjustments of acid-base changes by the respiratory mechanism are diminished or absent. Careful attention must be paid to intake and output—including feces, gastric aspiration, and sputum—to ensure optimal hydration, not only for preventing further pulmonary complications but also for providing efficient renal adjustment of electrolyte balance. Besides checking the acid-base balance, one must give close attention to frequent determinations of specific electrolytes in the patient's blood.

Infection

Adequate hydration, proper ventilation, and good nursing care are the most important factors in preventing infection. The presence of open wounds, a urinary-bladder catheter, and intravenous needles or catheters on a long-term basis tends to increase the risk of infection to the patient; and addition of the airway insult attendant with long-term ventilator therapy makes infection almost commonplace. It is important to manage this complication with great care, since frequently the indiscriminate application of broadly effective antibiotics promotes the growth of otherwise harmless inhabitants of their host, the patient. Scrupulous sterile technique in suction of the trachea and good isolation procedures on the part of the personnel and visitors will do the most in preventing these infections.

Nutrition

There seems to be a correlation between respiratory insufficiency and gastrointestinal insufficiency. Many of the patients who require respiratory assistance have ileus, from hypoxia, air swallowing, or over-distention of the stomach and small bowel caused by previous IPP breathing with a mask. In such cases it is important to institute gastrointestinal drainage by intubation and to supply the necessary fluid, electrolytes, and calories by the intravenous route. If muscular paralysis is not present, oral feeding may be started gradually when the ileus has resolved; or if swallowing is impossible, duodenal feeding of a suitable balanced mixture may be given.

NURSING CARE

The respirator patient presents a great challenge to the nursing personnel, and usually the response to this challenge is the single most

important factor in the outcome. The patients often are totally dependent on their respirator, and may well asphyxiate within five minutes in the event of an empty tank, a pulled plug, or a slipped connection. In our experience, this last difficulty seems the most common. Someone must always be at hand who not only is alert to any change in rhythm, pitch, tone, or volume of the respiratory cycle but who can restore normal operation promptly. *We consider fully automatic respirators dangerous from this standpoint, since many will continue with the same cycle despite obstruction of the airway, disconnection of fittings, or any change whatever in condition of the patient.* The alert nurse often can identify the need for readjustment of the apparatus from subtle changes in sound inaudible to others. Such service, through continuous attention, in addition to conscientious charting and reporting, cannot be overemphasized. We believe that the patient totally dependent on a respirator should never be left alone.

ETHICS

Usually the decision to start respirator therapy is an obvious one, based on clearly defined indications and directed toward a specific goal. Occasionally it may be arbitrary—the selection of the lesser of two evils. It even may be made by someone not directly concerned with the continuous care of the patient. In any event, when such therapy is undertaken there must be a responsible physician to oversee all of its administration. This physician may seek consultation from others, delegate responsibility for periods during which he will be absent, and make use of the ancillary services usually available in a modern hospital; but he ultimately must answer for the overall management of the ventilator patient.

It has been demonstrated repeatedly that automatic ventilators can prolong the life of patients otherwise moribund. Patients with irreversible damage to the central nervous system can be kept alive for weeks—even months—by this means. Although such heroic measures are difficult to defend from any standpoint, no one ever seems willing to be the one who chooses not to use a ventilator even under hopeless circumstances. Once such therapy has been started, however, there is a significant legal risk in discontinuing it on the basis of a hopeless prognosis alone. When the consensus of attending physicians is that there is no possibility of recovery, the consideration given to starting ventilator therapy should be very careful; for once it is begun, the doctor could face a serious criminal charge for stopping it while life exists.⁹

CONCLUSIONS

This discussion has been nonspecific, intended to touch upon the wide variety of different situations and adaptations of the ventilator treatment

of respiratory insufficiency. The subject reaches almost every medical discipline, and much is yet to be learned. We hope that those who become directly involved in this field will refer to the many monographs and articles^{2-5, 11-14} concerning each problem in detail, and that those whose practice is remote from this particular phase of medicine will comprehend better the many facets of this truly vital subject.

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Management of Patients with Pulmonary Insufficiency Undergoing Surgery

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While the application of current knowledge and techniques has greatly reduced the risks of surgical procedures in patients with respiratory insufficiency, these patients remain a major challenge to the surgeon and the anesthesiologist and to the internist who participates in the preoperative and postoperative care.

Whether a patient is to undergo surgery primarily for lung disease or for some other condition complicated by pulmonary insufficiency, problems of management fall into four phases. Obviously, the recognition of the nature of the disorder and the assessment of the pulmonary problem constitute an essential first step. From such knowledge the need for and type of preoperative preparation follow naturally, and then the selection of agents and procedures for anesthesia. Finally, postoperative re-evaluation of the patient and specific treatment—newly instituted or continuing—must be carried on through surgical convalescence and often beyond.

We shall attempt to outline the respiratory problems that may confront the candidate for surgery and to discuss the methods and techniques that have been developed to prepare the patient for his operation, to carry him through the actual procedure, and to help him through the postoperative period.

Respiratory insufficiency implies an inability of the lungs to exchange gases adequately to meet the needs of the body during effort. Respiratory failure denotes inadequate ventilation at rest. While respiratory insufficiency may be compensated for by reduced activity, increase of either stress or the restrictions on ventilation can produce respiratory failure and death. Major improvements in preoperative and postoperative care and in techniques of surgical procedures and anesthesia have decreased the risk of surgery for the respiratory cripple. However, pulmonary insuffi-

ciency remains a threat to survival and must be carefully managed before, during, and following any operative procedure.

PREOPERATIVE ASSESSMENT

Evaluation of the nature and extent of the pulmonary problem requires clinical judgment in addition to objective evidence. Dyspnea upon exertion, the commonest sign of respiratory distress, often has non-pulmonary causes. Heart disease such as valvular abnormalities, myocardial ischemia, or cardiac decompensation either improves with appropriate treatment or permits reasonably accurate estimation of risk. Anemias causing dyspnea can be corrected preoperatively by transfusions of whole blood or packed red blood cells. Similarly, dyspnea associated with metabolic disturbances such as hyperthyroidism, diabetes mellitus, and so on must be recognized and met with appropriate measures.

Dyspnea results from numerous ventilatory abnormalities. Muscular defects of the thorax, including poliomyelitis, myasthenia gravis, and traumatic quadriplegia, often require mechanical support of ventilation during and after surgery plus drug therapy as applicable. Restrictive conditions such as obesity, rheumatoid spondylitis, kyphoscoliosis, pleural thickening, pulmonary fibrosis, and emphysema pose mechanical limitations of ventilation which surgical dressings or restrictive body positions may accentuate postoperatively. Dyspnea due to diffuse obstruction of the airway, resulting from bronchiolar spasm of asthma or emphysema or from the presence of widespread, tenacious secretions of chronic bronchitis or bronchiectasis, is usually amenable to therapy prior to surgery.

Estimation of tolerance for exercise is an important preoperative procedure. Stair climbing or simple movements during examination often quantitate ventilatory impairment well. Attention to the degree and symmetry of chest expansion, the volume of breath sounds, the presence of wheezing or stridor, and distention in the veins of the neck adds valuable information. Recognition of respiratory distress in the horizontal position—whether supine, prone, or lateral—helps to modify posture on the operating table to the benefit of the patient.

Thoracic roentgenograms should be made routinely of all candidates for surgical procedures. Fluoroscopy may help further in evaluating pulmonary disability.

Objective measurements of pulmonary function clarify the type and degree of insufficiency. The vital capacity, maximal breathing capacity, residual volume and its relation to total volume, arterial oxygen saturation, and carbon-monoxide diffusion all are helpful parameters; and sometimes the electrocardiogram serves likewise. Bronchspirometry may be helpful if resection of pulmonary tissue is contemplated. Although the data obtained are only guides, a maximal breathing capacity of less than 50 per

cent foretells a difficult postoperative course and argues against pulmonary resection.

It is imperative that the patient himself have a clear understanding of his pulmonary problem and that he cooperate fully in preoperative preparation and postoperative care. If tracheotomy is likely, its advantages should be discussed.

PREOPERATIVE CARE

In the presence of pre-existing respiratory insufficiency, acute infections of the respiratory tract are potentially fatal; their presence contraindicates elective surgery and demands aggressive treatment. Weight reduction is indicated in obesity and metabolic disorders should be corrected as well as possible before operation. While mechanical conditions such as spondylitis or neuromuscular disease of the chest wall or diaphragm may improve only minimally with preoperative efforts, training the patient in the use of ventilatory assisters will aid in postoperative care.

Chronic cough merits preoperative preparation. Use of tobacco should be stopped completely. Respiratory irritants and known offending allergens should be avoided. Dust-control measures are beneficial. The unnecessary cough should be suppressed; but when tracheobronchial secretions are present, they should be liquefied. Iodides, ammonium chloride, and guaiacol derivatives plus copious fluid intake aid in loosening secretions so that cough will be effective. Aerosols of water or saline or heated-mist inhalations are useful; the addition of detergents or enzymes is seldom needed for liquefying sputum.

Patients with asthmatic bronchitis or pulmonary emphysema often benefit from hospitalization to facilitate preparation for surgery. Control of cough, liquefaction of sputum, knowledge of inhalation techniques, and familiarity with intermittent positive-pressure devices (such as flow-sensitive valves) for administration can be attained more effectively by hospitalized patients than by outpatients.

When bronchopulmonary suppuration is present, preoperative use of antibiotics may be indicated. Cultures and sensitivity tests can identify the offending organism and indicate proper treatment. Often the use of a broadly effective antibiotic such as tetracycline for five or six days before operation will be adequate. As a rule, penicillin should be used only if the principal organism is a streptococcus or *Diplococcus pneumoniae*. The type of organism may indicate other drugs such as erythromycin, streptomycin, chlortetracycline, chloramphenicol, polymyxin, or colistimethate (Colmycin). Administration of antibiotics by inhalation may be helpful: for example, streptomycin or neomycin may be given by aerosol in doses of 200 mg./ml. four times daily. Polymyxin in doses of 10 to 20 mg./ml. may

be administered by aerosol inhalation if pseudomonas organisms are present in respiratory-tract secretions.

Steroid compounds are often beneficial in preparing the pulmonary cripple for operation. In patients who have taken steroids continuously or intermittently during some period before surgery, extra medication may be indicated to support adrenal function during and after the operation. Additionally, in patients with severe asthmatic bronchitis steroid therapy often eases the bronchospasm and controls secretions sufficiently to permit surgery. Likewise, some patients who have pulmonary fibrosis or interstitial pneumonitis associated with diseases such as the Hamman-Rich syndrome or sarcoidosis may have pulmonary function improved by steroid therapy.

The location for the contemplated surgical procedure is important in assessing the significance of ventilatory insufficiency. Operations on the head, neck, extremities, and perineum have little effect upon ventilation. However, abdominal operations, flank procedures, and operations involving the rib cage often restrict ventilation by visceral packs, abdominal distention, tight dressings, or inspiratory pain; and they may limit or prevent coughing. Operations on the heart and esophagus which interfere minimally with the movements of the chest wall and diaphragm are usually well tolerated. When pulmonary resection is intended, consideration must be given to the adequacy of the remaining lung tissue and to the temporary crippling of the respiratory effort in the ipsilateral lung. Although the lung tissue remaining after lobectomy expands to provide the best prosthesis for the thoracic space, its function often is seriously impaired.

ANESTHETIC MANAGEMENT

After careful preoperative evaluation and preparation, the anesthetic must be managed so as to produce adequate operating conditions with the least possible drug impairment of the vital functions of the patient. Following administration of the anesthetic, the patient should resume vigorous spontaneous control of his vital functions at the earliest possible moment.

Premedication should be selected for each patient individually. In the absence of pain, opiates are of little value, since their side effects include circulatory instability and impaired ventilatory response to increased tensions of carbon dioxide. Tranquillity can be produced in a high percentage of patients by judicious doses of barbiturates or related compounds. Atropine or scopolamine can be of use in controlling bronchial secretions. Scopolamine has less effect on reflex parasympathetic phenomena affecting the heart and lungs, but also has less tendency to produce tachycardia than does atropine.

The location and duration of intended surgical procedure usually dictates the method of administering anesthesia. Conduction anesthesia is

effective for surgery on the extremities and perineum as well as certain areas of the surface of the trunk and head. The respiratory cripple, however, often requires active expiration using abdominal muscles to assist; thus relaxation of the abdominal wall is detrimental to his ventilation. Consequently, spinal anesthesia for an abdominal procedure may be just as hazardous as carefully administered general anesthesia—and without the added comfort of sleep for the patient.

Most general anesthetic agents are acceptable for the pulmonary cripple. An exception might be cyclopropane, a flammable bronchoconstrictor which could be detrimental to the asthmatic or hazardous in the presence of cautery. Halothane, a newer agent, is potent, rapid-acting, nonirritating to the respiratory mucosa, and nonflammable. It tends to increase pulmonary compliance—probably in part by relaxing respiratory smooth muscle. The analgesic potency of ether, its minimal cardiovascular depressant effect in light levels of anesthesia, its tendency to combat bronchospasm in the asthmatic, the high percentage of oxygen with which it can be used, and its ease of administration make it still a useful agent for intrathoracic surgery. Flammability, of course, is its drawback. Thio-pental (Pentothal), given in small doses intravenously, is a useful agent for induction.

Ventilatory support must be maintained throughout anesthesia and into the postanesthetic period until the patient can resume adequate spontaneous ventilation. Ordinarily an endotracheal tube is useful in patients with prior ventilatory deficiency, though occasionally one with a marked tendency toward bronchospasm may react adversely to this foreign body. The tube supports the upper part of the airway and decreases anatomic dead space. Control or assistance of ventilation, either by manual techniques or by a carefully supervised automatic ventilator, overcomes the depressant effect of anesthetic agents and premedicant drugs. Though inflation of the lungs can be augmented thus, deflation under anesthesia is usually a passive phenomenon of the recoil of the lung tissue and chest wall. Thoracic fixation and air trapping impair deflation and are difficult to manage. High residual volume, poor mixing of pulmonary gases, and slow induction and emergence from anesthesia result. Application of sub-atmospheric pressure ("negative pressure") to the airway may decrease intrathoracic pressure centrally prior to alveolar emptying and increase the degree of air trapping.

Sometimes operating positions needed for surgical exposure further upset already impaired ventilation. This is most likely to occur in the lateral position with the kidney rest elevated, in the prone position, in the lithotomy position, and in the steep Trendelenburg position. When pulmonary embarrassment is evident, these positions may have to be modified to permit effective ventilation during anesthesia.

For enabling the pulmonary cripple to regain control of vital functions at the earliest possible moment after operation, the manner in which

anesthesia is maintained has great importance. To assure uncomplicated recovery from anesthesia, the amounts of anesthetic agents and muscle relaxants must not be excessive and observation of the patient must be constant. Airway secretions must be aspirated carefully, coughing must be encouraged, and muscle tone to support adequate spontaneous ventilation must be restored. Routine postoperative chest roentgenography provides information about unsuspected chest pathology incidental to surgery or anesthesia such as pneumothorax, hemothorax, or atelectasis. High oxygen tensions in humidified air should be provided.

Removal of the endotracheal tube requires careful consideration, since its absence increases the anatomic dead space, withdraws support of the upper airway, and makes aspiration of intratracheal secretions more difficult. A tracheotomy may be necessary to permit effective ventilation and should be performed at the first indication of its need. Cuffed tracheostomy tubes are available so that mechanical ventilators may be used if necessary. Bronchodilators are helpful if expiratory slowing is a factor and may be given either intravenously or by nebulization. Heated-mist units can provide adequate airway humidification for tracheotomized patients and should be employed.

POSTOPERATIVE MANAGEMENT

The most critical period in the management of patients with pulmonary insufficiency comes immediately following operation, when the patient must depend upon recovery of his own capabilities for continued ventilation and airway patency. Obviously, all the preceding phases of assessment, treatment, and management have been directed to restoration of these natural resources to the maximum feasible. The anticipation of the specific needs of a given patient is an essential factor in the success of this transition. Equally important, however, is the hour-to-hour and day-to-day reassessment of the patient in this early period. It is during this time too that not only the respiratory cripple, but even the patient with normal pulmonary reserve, may suddenly experience decompensation.

It is senseless, of course, to sharply divorce observations of the respiratory system from observations of the patient as a whole. Skin color and temperature, state of consciousness, quality of peripheral pulses, pulse rate, blood pressure, and even urinary output are valid indices of pulmonary function, as they are of cardiovascular, central nervous system, and urinary function. Although radiographic examination of the thorax is of inestimable value in assessing the thorax and its contents, simple bedside examination is indispensable. Tidal exchange of gases by the lung can be assessed effectively by auscultation of the lungs and by observation of the force and volume of expiration and of the degree and effort of thoracic excursions. Poor respiratory exchange has many causes; and if not correctable by

simple or expedient means, it is the major indication for use of a mechanical ventilator in the postoperative period.

Anticipation of the need for assistance in eliminating tracheobronchial secretions is essential in avoiding potentially lethal episodes of pulmonary atelectasis and anoxia among patients with already compromised pulmonary reserve. On occasion, bronchoscopy will be required to remove thick, tenacious secretions or coagulated blood from the tracheobronchial tree. Frequent or ineffective nasotracheal aspiration is often a valid indication of the need for tracheostomy. Problems with airway patency and poor ventilation are so often associated that the cuffed tracheostomy tube should be inserted even though there may be no immediate or anticipated need other than to decrease the respiratory dead space and create a convenient stoma for tracheobronchial aspiration. Later, if needed, the balloon cuff of the tracheostomy tube can be inflated for use with an intermittent positive-pressure apparatus.

The ultimate effectiveness of respiration in terms of tissue oxygenation and elimination of carbon dioxide depends, of course, on adequate perfusion of the lung and the other organs and tissues of the body. The maintenance of nutrition, blood volume, hemoglobin, and fluid and electrolyte balances is mundane but essential in the care of any surgical patient; but it assumes critical proportions in the management of the patient with an already compromised respiratory reserve.

Bronchodilators, agents that liquefy tracheobronchial secretions, humidification, high oxygen tensions in inspired gas mixtures, and the intermittent positive-pressure respirator all are important factors in postoperative management of the patient with respiratory insufficiency, in addition to whatever measures may have been initiated preoperatively. A high-oxygen environment, though desirable in many situations, may precipitate carbon-dioxide narcosis in the patient with pulmonary insufficiency and respiratory acidosis. Often postoperative analysis of the partial pressure of carbon dioxide, pH, and buffer base is essential for the recognition and treatment of respiratory and metabolic aberrations in acid-base balance.

The use of analgesics in the patient with respiratory insufficiency is also a critical postoperative problem. Although age, sex, weight, and vigor influence the usual dosage of these agents, their specific depressant effects on the cough reflex and respiratory center may be hazardous to the respiratory cripple. However, even such a potent agent as morphine, if given in a minimal dose of 1 mg. (1/65 grain), will often effect worthwhile prolonged analgesia and tranquillity without undue depression. In cases of respiratory insufficiency, it is probably not wise to have any narcotic agent administered at regular intervals by the nursing staff: re-evaluation with each administration is best.

Occasionally, regional nerve block can be used as an effective means to control incisional pain and thereby improve ventilation and decrease the need for narcotics. Surgical dressings may restrict ventilatory motion

and should be applied with the avoidance of this effect in mind. The prevention or correction of abdominal distention in the postoperative period has a similar desirable influence on pulmonary ventilation. Maintenance of pulmonary expansion following operations within the thorax is essential. Intercostal drainage tubes placed in the thorax at the time of surgery to evacuate air and fluid require continued maintenance in the postoperative period to assure their continued function. This maintenance and the eventual removal of the tubes should not allow the introduction of infection into the pleural space nor the accidental introduction of air. Repeated radiographic examination of the thorax is needed to assess the adequacy of pleural-space drainage.

Pulmonary edema, congestive heart failure, and cardiac arrhythmia are not uncommon as postoperative complications of older patients and those with pulmonary insufficiency. Cardiac arrhythmias occur more frequently in patients undergoing intrathoracic procedures than in those undergoing surgery on the abdomen, head and neck, or extremities. Since such problems cannot always be anticipated by preoperative assessments, careful observation is essential in the postoperative period.

COMMENT

It is obviously beyond the scope of this presentation to give in detail the management of all complications or even to list all the means currently available for assessing and treating the complications peculiar to management of patients with pulmonary insufficiency. The essential features of good management, however, are awareness of potential difficulties and diligence in seeking, assessing, and treating these problems.

At the completion of a successful postoperative hospital convalescence, the need for continuation and supervision of treatment must be assessed. Finally, the patient and his relatives must be informed of both the necessity for these measures and the need for their cooperation and understanding of the proposed long-term program.

SUMMARY

Patients with asthma, emphysema, pulmonary fibrosis, bronchopulmonary infections, and various other disorders which interfere with the normal function of the lungs may be candidates for surgical treatment. It is important that the cause of the pulmonary disorder be identified and that risks attributable to the respiratory deficiency be properly assessed. Preoperative preparation depends, of course, upon the nature of the pulmonary disturbance. Appropriate antibiotic therapy should be given for bronchopulmonary infection. Aerosol techniques are available for the

management of bronchospasm and for the liquefaction and elimination of tracheobronchial secretions. Even steroids have their place in the preparation of some patients.

The anesthesiologist must be thoroughly familiar with the nature of the pulmonary problem. He should choose the optimal premedication for the individual patient. The selection of the anesthetic and the method of its administration will be determined not only by the needs of the surgeon, but also by the ventilatory problems of the patient, and especially by the desirability of early recovery of his ability to carry on his own breathing.

Many of the measures instituted in the preoperative preparation should be continued in the postoperative period. Because of the need for analgesics and sedatives, the problem of retention of secretions deserves special attention. If the patient is unable to cough up his secretions, mechanical aids such as the intratracheal catheter or even bronchoscopic aspiration must be employed. Tracheostomy is often advantageous, not only for elimination of secretions but also to cut down on the dead space. Mechanical assistance, usually employing flow-sensitive pressure valves, may help the patient with ventilatory problems. Oxygen, heated mist, and bronchodilators may be administered by positive pressure as well as by simpler techniques.

Through the cooperative efforts of the surgeon, anesthesiologist, and internist, many respiratory cripples can undergo major as well as minor surgical procedures.

Air Transportation of Patients with Pulmonary Disease

EARL T. CARTER, M.D., PH.D.

MATTHEW B. DIVERTIE, M.D.

The advent of turbojet power has enabled commercial airliners to take advantage of the diminished turbulence and air friction in the thinner air between 30,000 and 40,000 feet in order to achieve smoother and faster flight. The increased use of commercial airliners flying at this altitude and the widespread acceptance by the public of this form of travel have introduced problems relating to pulmonary disease which a physician may be called upon to answer.^{5, 9}

Even individuals maximally acclimatized to inhabitable altitudes could not long endure exposure to the flight altitudes attained by a modern jet. Consequently measures must be taken to protect the individual from changes in his environment which otherwise would endanger his life. The most suitable method is pressurization of the cabin. Exposure to altitude produces acute hypoxia due to breathing air with a reduced partial pressure of oxygen. In young healthy adults the first objective symptoms usually occur at an altitude of about 10,000 feet and consciousness is lost at approximately 23,000 feet.¹⁰ The insidiousness of the onset of symptoms of hypoxia during ascent to high altitudes is one of its greatest dangers. In commercial jet-powered airliners, sea-level pressure can be maintained in the cabin up to an altitude of about 25,000 feet; and at 35,000 feet the cabin pressure will not drop below that equivalent to 8,000 feet. A normal individual at rest in such an airplane can compensate adequately for the slight reduction in the partial pressure of oxygen in his environment.⁸

PHYSIOLOGIC CONSIDERATIONS

The shape of the oxygen dissociation curve is related to some interesting effects that occur with ascent to flight altitude (Fig. 1). The nearly flat upper portion of the curve signifies that arterial saturation of oxygen

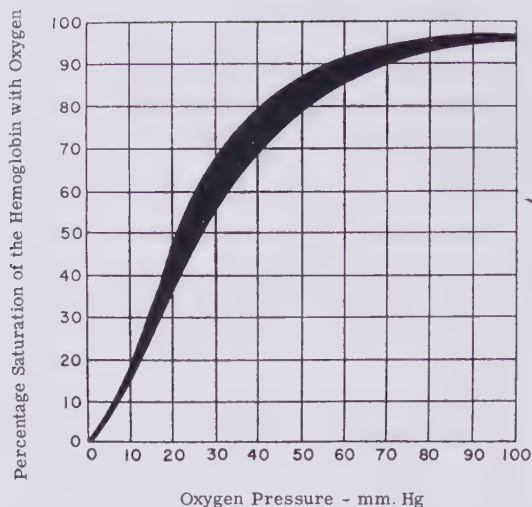


Figure 1, The oxygen dissociation curve for human hemoglobin.

declines much less than its arterial partial pressure in the range from 100 to 60 mm. Hg. Below that point, however, the slope of the curve increases. This may seem a disadvantage at first glance; but in the hypoxic state associated with exposure to altitude above 10,000 feet, it is this characteristic that permits adequate extraction of oxygen from the blood by the tissues for a relatively small decline in partial pressure of oxygen. This effect tends to defend the tissue partial pressure of oxygen as the alveolar partial pressure of oxygen declines.

At sea level, the oxygen tension of the inspired air is more than 142 mm. Hg and arterial oxygen saturation at normal temperature and pH is greater than 95 per cent, which corresponds to an arterial oxygen tension of 95 mm. At an altitude of 6,000 feet above sea level, the barometric pressure is 600 mm. Hg and the inspiratory oxygen tension is reduced to 116 mm. With normal alveolar carbon-dioxide tension and a respiratory quotient of 1, the alveolar oxygen tension in these circumstances is 76 mm. Hg, which is sufficient to ensure near-normal arterial oxygen saturation while at rest. Under similar conditions at an altitude of 10,000 feet, the alveolar oxygen tension is reduced to about 60 mm. Hg and the peripheral arterial saturation is about 88 per cent.¹⁰ With increasing altitude, gas exchange occurs on the steeper part of the curve and arterial oxygen saturation diminishes more rapidly per unit of fall in partial pressure of oxygen. This detrimental effect of the shape of the curve is offset by the benefit to tissue oxidation already described.

It is also of interest to consider the effect of exercise at altitude. Exercise increases the gradient between the partial pressure of oxygen in pulmonary alveoli and that in pulmonary capillary blood. The rise in alveolar partial pressure of oxygen subsequent to hyperpnea is one factor tending to compensate for this change as well as an increase in the pul-

monary capillary perfusion rate. Thus, during moderate exercise at sea level, no significant fall in arterial partial pressure of oxygen is observed. At altitude, however, even at rest there is already a primary reduction in alveolar partial pressure of oxygen and a hyperventilatory state. The influence of altitude on the adjustments to exercise has been demonstrated in a decompression chamber at a simulated altitude of 6,000 feet.² The experimental subjects manifested a decline in arterial oxygen saturation subsequent to exercise at altitude, an effect not observed at sea level. Since the pulmonary ventilation equalled the summed effects of both hypoxia and exercise, the ventilation was greater than that necessary to eliminate the metabolically produced carbon dioxide alone. Accordingly, a state of hypocapnia resulted. Hypocapnia tends to hamper the dissociation of oxyhemoglobin in the tissues but augments the association of oxygen with hemoglobin in the lungs.⁶

In addition to the mechanisms already described, a compensatory increase in cardiac output is important in the maintenance of tissue oxidation at increasing altitude. With increased perfusion of tissues, oxygen extraction per unit volume of blood decreases. This has the effect of attenuating the fall in the partial pressure of oxygen of the blood as it traverses the capillaries, and thus it helps to lessen the need for lowering of the tissue partial pressure of oxygen.⁶

The amount of oxygen delivered to the tissues is a function of the cardiac output (C.O.) and the oxyhemoglobin concentration (HbO_{2a}). Where the cardiac output is expressed in liters per minute and oxyhemoglobin concentration is expressed in volumes per cent (ml./100 ml. blood), the quantity of (arterial) oxygen delivered to the tissues is:

$$\text{C.O.} \times 10 \text{ HbO}_{2a} = \text{ml./min.} \quad (1)$$

But the rate at which oxygen actually is extracted by the tissues to satisfy metabolic needs—that is, the metabolic rate—is not determined solely by the oxygen delivery. Hence it is better to deal with the oxygen extraction or metabolic rate itself ($\dot{V}_{\text{O}_2}$):

$$\dot{V}_{\text{O}_2} = (\text{O}_2 \text{ delivered to tissues}) - (\text{O}_2 \text{ returned to lungs}). \quad (2)$$

This equation can also be written as:

$$\dot{V}_{\text{O}_2} = (\text{C.O.} \times 10 \text{ HbO}_{2a}) - (\text{C.O.} \times 10 \text{ HbO}_{2v}) \quad (3)$$

where HbO_{2a} and HbO_{2v} represent the oxyhemoglobin concentrations of the arterial and mixed venous bloods, respectively. Both C.O. and $\dot{V}_{\text{O}_2}$ are expressed in milliliters per minute.

Equation (3) can be rearranged:

$$\dot{V}_{\text{O}_2} = 10 \text{ C.O.} (\text{HbO}_{2a} - \text{HbO}_{2v}) \text{ ml./min.} \quad (4)$$

This will be recognized as the Fick principle. It shows that the metabolic

rate can be expressed in terms of the cardiac output and the arterial-venous difference of HbO_2 . The fact that this difference under basal conditions is normally 5 volumes per cent does not imply that adequate oxygen extraction by the tissues can be accomplished so long as the HbO_{2a} is greater than 5 volumes per cent. The HbO_{2v} is a function of the venous oxygen tension, which depends in turn on the tissue oxygen tension. In order for internal respiration to continue, the tissue oxygen tension must be maintained at a minimal value. As a practical guide based on altitude tolerance studies on normal individuals,^{8, 10} 13 volumes per cent may be accepted as the minimal permissible HbO_{2v} for prolonged exposure to altitude, corresponding to a partial pressure of oxygen (P_{O_2}) of about 34 mm. Hg and an HbO_2 saturation of 65 per cent.

This being the case, we can rewrite equation (4) as:

$$\dot{V}_{\text{O}_2} = 10 \text{ C.O. } (\text{HbO}_{2a} - 13) \quad (5)$$

Equation (5) thus applies only to normal or acceptable conditions for indefinite exposure to altitude. Altitudes resulting in a mixed-venous oxyhemoglobin concentration of less than 13 volumes per cent are to be considered unsafe.

Taking the normal arterial-to-venous oxygen difference to be 5 volumes per cent, equation (5) indicates that if the HbO_{2a} falls below 18 volumes per cent (corresponding to a P_{O_2} of about 60 mm. Hg, or a peripheral arterial oxygen saturation of 88 per cent) a rise in cardiac output will be required for support of normal oxygen extraction by the tissues, $\dot{V}_{\text{O}_2}$. If 250 ml./min., STPD, is assigned for the normal basal metabolic consumption of oxygen, equation (5) can be rewritten as follows:

$$\text{C.O.} = \frac{250}{10 (\text{HbO}_{2a} - 13)} \quad (6)$$

Equation (6) now describes the relationship between the C.O. and the HbO_{2a} which is required to maintain the HbO_{2v} at no less than 13 volumes per cent and the $\dot{V}_{\text{O}_2}$ at 250 ml./min.

Should there be sufficient hypoxia to reduce the arterial oxygen content below 18 volumes per cent, equation (6) can be used to calculate an adequate value for C.O. (Table 1).

The minimal acceptable conditions of an arterial oxyhemoglobin content of 18 volumes per cent and a venous content of 13 volumes per cent are found in the average healthy individual at an altitude of about 10,000 feet while breathing air.^{8, 10} As the saturation of arterial blood lessens, larger and larger increases in cardiac output are required for maintaining normal oxygen supply to the tissues. The 25 L./min. which the 70 per cent saturation at 18,000 feet makes necessary for maintenance of the basal state of metabolism is a severe demand. Experimental observations have shown that it is not met: the partial pressure of oxygen in the tissue and in the mixed venous blood falls below tolerable levels, with

Table 1. *Relationship Between Cardiac Output and Arterial Oxyhemoglobin Concentration Required for Adequate Mixed-Venous Oxyhemoglobin and Basal Metabolic Rate*

APPROXIMATE ALTITUDE (ft.)	HbO _{2a} (volume per cent)	SATURATION (per cent)	C.O. (L./min.)
10,000	18	88	5.0
14,000	17	80	6.3
16,000	15	75	12.5
18,000	14	70	25.0

resultant serious impairment of body function. It is to be emphasized that the data in Table 1 are applicable for the basal state only, and that metabolic demands above this level require a cardiac output in excess of those tabulated. In actuality, healthy individuals resting quietly at an altitude of 8,500 feet demonstrate an increase in cardiac output of approximately 25 per cent.⁸

CLINICAL CONSIDERATIONS

The experience of the Military Air Transport Service has shown that almost every patient suitable for transportation by surface route may be transported with equal safety by air, provided that proper facilities are available. The journey by air usually is more comfortable for a seriously ill patient. For patients with respiratory disease, consideration must be given to the physical properties of the gases of the environment and to the severity of disturbance of the patient's physiologic responses.

The physiologic effects of high-altitude exposure are related closely to the physical behavior of the gases at these levels. Along with the reduction in pressure and in oxygen tension at higher altitudes, there is also a decrease in air density. This interferes with the cough mechanism by leading to a reduction in the expiratory pressure and flow rate that can be developed at the time of the expulsive cough.¹³ On the other hand, the lesser density of air reduces the work of breathing—an advantage to patients with increased airway resistance.¹² During performance of the maximal breathing capacity test at sea level, a predominantly turbulent flow through the airways is developed because of the high flow rates. Findings from 13 healthy adult males at various altitudes are shown in Figure 2.³ From this it can be seen that the mean values for maximal breathing capacity increase as the air pressure lessens with increase of altitude. The effect is similar to that in the breathing of low-density helium at ground level, where turbulent airway flow is converted to a laminar pattern. Because of this the emphysematous patient may be aware

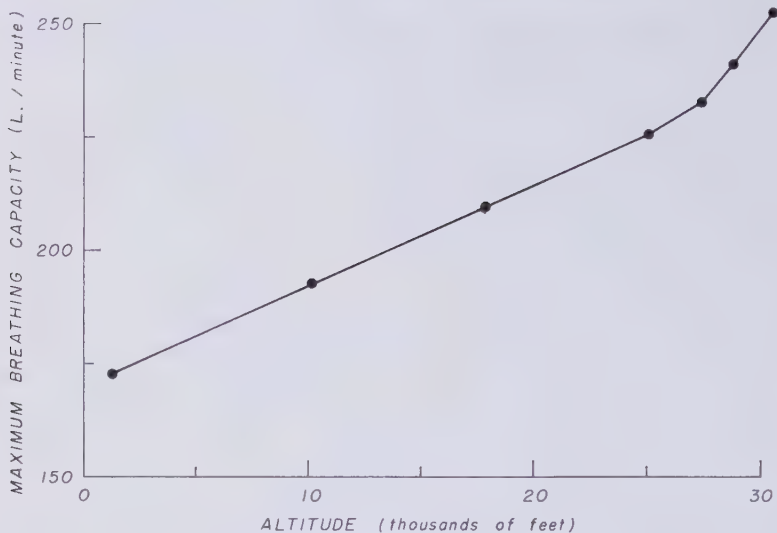


Figure 2. Mean values for maximal breathing capacity in 13 subjects breathing oxygen at increasing altitudes.

of an improvement in the mechanical effort of breathing, but secretions are less readily expelled in this and other pulmonary conditions.

Trapped gases expand as altitude increases and the outside pressure falls. Pain due to the expansion of gas trapped in a hollow abdominal viscus or in the middle ear is troublesome and can be relieved only by escape of the gas. In the thorax, expansion of air present in a cyst or pneumothorax or closed in after lobectomy or pneumonectomy may have serious and possibly fatal consequences (Fig. 3).⁴ For air transport of patients with conditions such as this and others of similar severity, it is important that a trained nurse or a physician be present throughout the journey in case unusual attention should be necessary.

The presence of pulmonary tuberculosis in an active stage or of any other infectious disease is a contraindication to air travel in the company of other passengers and is prohibited by law. Pulmonary suppurative disease or a serious or disabling condition that might be upsetting to other travelers should be accepted as a strong deterrent to transport by commercial airliner but need not prevent transportation by a suitably equipped private plane or by air ambulance.

The committee on physiologic therapy of the American College of Chest Physicians has pointed out that altitude produces very serious aggravation of existing disabilities in the presence of carbon-dioxide retention or marked alveolar capillary block.¹ The patient who is unable to hyperventilate to compensate for carbon-dioxide retention or for the reduced partial pressure of oxygen at high altitudes presents a serious problem.^{1, 7}

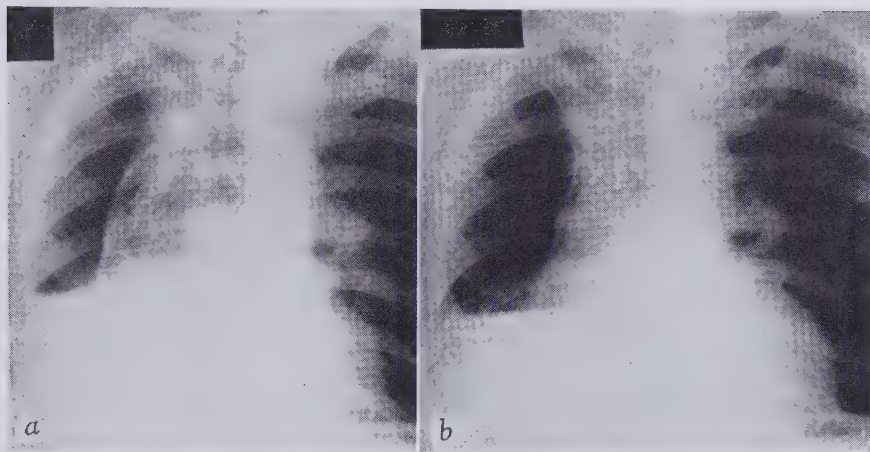


Figure 3. *a*, Thoracic roentgenogram of patient with right-sided hydropneumothorax at sea level. *b*, Same patient exposed to altitude of 8,000 feet, showing considerable expansion of trapped gas.

Shillito and associates, in a study of ambulatory patients with chronic noninfectious pulmonary disease, found that a maximal breathing capacity of less than 40 L./min. and arterial oxygen saturation of less than 90 per cent at sea level indicated intolerance to moderate-altitude exposure. A patient with pulmonary emphysema and an arterial oxygen saturation of 88 per cent is physiologically at an altitude of 10,000 feet even when he is resting at sea level. For him, ascent to 8,000 feet in the pressurized cabin of an airliner would be equivalent to ascent above 10,000 feet for an individual with normal lungs. That such a patient can safely maintain an adequate cardiovascular and respiratory response to such a stress is most unlikely.

Hypoxemia resulting from alveolar capillary block or from restrictive ventilatory disease, such as pulmonary or pleural fibrosis, may be relieved by administration of oxygen. In pulmonary emphysema, however—and especially if carbon-dioxide retention occurs—the dangers of oxygen therapy without the use of an intermittent positive-pressure breathing apparatus are well known. Federal regulations require that oxygen be carried on all planes flying above 8,000 feet, regardless of whether they are pressurized. This store of oxygen is intended for emergency purposes and is not usually sufficient to maintain therapy for a patient over any appreciable length of time in addition to its basic purpose. When a patient is to travel by air and requires oxygen to help him do so, a supply of oxygen, a reducing valve, and a mask should accompany him for his use.

No patient with major cardiopulmonary disease should be exposed to a cabin altitude greater than 8,000 feet. The presence of cyanosis imposes a 6,000-foot ceiling, and acidosis complicating emphysema should limit the patient to a maximal altitude of 4,000 feet in a pressurized cabin

or in a nonpressurized plane. Cor pulmonale imposes a similar restriction, and markedly reduced respiratory reserve accompanied by tachycardia at ground level is an unfavorable prognostic index for even short-term exposure to moderate cabin altitudes.^{1, 7, 15}

Although acute respiratory illness is a contraindication to travel by air (unless other medical factors require it), the transport of patients with chronic respiratory disease demands an evaluation of the physiologic status as has been suggested. Pulmonary function tests provide objective measurement of the derangements. In particular the peripheral arterial oxygen saturation and the maximal breathing capacity are of major importance in assessing the presence and degree of hypoxemia and the ability of the patient to hyperventilate.¹

If facilities for such tests are not available, the physician must depend on the more traditional clinical examination of the patient. The presence or absence of cyanosis and of ability to increase voluntary ventilation are fundamental in the clinical assessment of respiratory reserve. Ability to blow out a match and to climb a flight of stairs has provided useful indices in the past and will continue to be helpful as rough measures.¹¹ Even though a patient has lost ability to compensate for his pulmonary disease by hyperventilation he may still fly if adequate facilities, including a supply of oxygen, are available to him and if an attendant accompanies him. Since the major effect of high-altitude exposure falls on the respiratory system, the physician who concerns himself with the care and treatment of such diseases should be familiar with the problems involved.

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The Role of the Personal Physician in the Eradication of Tuberculosis

DAVID T. CARR, M.D.

America's physicians should be proud of the part that they have played in the battle against tuberculosis. The struggle which has been waged by many organizations and individuals has resulted in remarkable progress against this disease. At the beginning of the twentieth century, it was the most common cause of death in the United States with mortality estimated to have been about 200 per 100,000 persons per year. By 1960 tuberculosis had fallen to sixteenth place among the causes of death and the mortality was only 6.1 per 100,000 persons per year.

In spite of this progress the disease is not yet conquered, and America's physicians cannot afford to rest on their laurels. The magnitude of the remaining problem of tuberculosis has been summarized in a recent publication of the U.S.P.H.S.¹ Table 1, taken from that publication, gives new active case rates and death rates for the years 1953 through 1961, the latest year for which complete figures were available. The new active case rate has dropped substantially during the nine years, but the rate of decrease is less for the more recent years. The death rate has decreased more than the new active case rate, but it too has declined more slowly in recent years. Other data collected by the U.S.P.H.S. indicated that as of December 31, 1960, there were approximately 120,000 known active cases of tuberculosis on case registers of the various health departments plus an additional 210,000 other cases not classified as active. Obviously there is much more work to be done.

The Arden House Conference on Tuberculosis of 1959² recommended an intensification of the battle against tuberculosis, particularly the mobilization of resources for adequate chemotherapy of all persons with active tuberculosis and those with inactive disease who are in danger of relapse.

More recently the National Tuberculosis Association has changed its goal from "The Control of Tuberculosis" to "The Eradication of Tuberculosis"; and a committee of the National Tuberculosis Association, with representatives from the National Conference of Tuberculosis Workers and the American Thoracic Society, have recommended a program of anti-

Table 1. *New Active Tuberculosis Cases and Deaths, United States, 1953-1961**

YEAR	NEW ACTIVE CASES		TUBERCULOSIS DEATHS	
	Number	Rate†	Number	Rate†
1953	84,304	53.0	19,707	12.4
1954	79,775	49.3	16,527	10.2
1955	77,368	46.9	15,016	9.1
1956	69,895	41.6	14,137	8.4
1957	67,149	39.2	13,390	7.8
1958	63,534	36.5	12,417	7.1
1959	57,535	32.5	11,474	6.5
1960	55,494	30.8	10,866	6.0
1961	53,726	29.4	9,938	5.4

* Reproduced with permission from Department of Health, Education and Welfare, Public Health Service, Communicable Disease Center, Tuberculosis Program, Atlanta, Georgia: Tuberculosis in the United States—Status of the Disease in the Early Sixties. (Public Health Service Publication No. 1036.) Washington, D.C., U. S. Government Printing Office.

† Per 100,000 population as of July 1.

tuberculosis activities that could lead to the eradication of this disease (see Appendix).

The success of this program of work in the anti-tuberculosis battle is completely dependent on the cooperation and dedication of America's physicians. This includes those in private practice as well as those in public offices such as public health departments, tuberculosis clinics, and tuberculosis hospitals. Let us review the program and determine the function of the personal physician in this campaign against tuberculosis.

It is obvious that all persons with active tuberculosis should have adequate treatment for their disease. Most patients—and especially those with contagious forms of tuberculosis—should and do enter tuberculosis hospitals for such treatment. The personal physician frequently is the one to whom the patient turns for advice about this decision. Unless there are unusual circumstances which warrant treatment outside of the hospital, the personal physician can do his patient no greater favor than to urge him to enter the hospital for treatment. After the patient has done so, the physician should keep in touch with him and his family and urge him to remain in the hospital until he has received the maximal benefit from treatment there. Obviously the duration of such hospital treatment will vary with such factors as the extent of the disease, the response to therapy, the concomitant diseases, and the adequacy of the home to which the patient can return.

After the patient is discharged from the tuberculosis hospital, the personal physician may become responsible for supervision of the anti-tuberculosis chemotherapy which may be needed for many months or years. The personal physician may also be responsible for regular follow-up

examinations for the rest of the patient's life. Only if this is faithfully done will relapse of the disease, if it occurs, be detected as early as possible and risk of spread of the infection be minimized. The rate of relapse following adequate modern treatment is not yet known, but we can not assume that these patients are completely cured and omit careful follow-up examinations.

The role of the personal physician is even greater in tuberculosis case-finding than in treatment. Every physician should be highly alert for tuberculosis and look for any evidence of it in every patient. This is of double importance because of the availability of excellent treatment for the disease and the contagiousness of most cases of tuberculosis.

The priorities assigned to various items listed under Case Finding in the Appendix may not be of great importance to the personal physician in his daily practice, but he may have a part in most of the activities under this heading. He can be of great help in the prompt examination of all contacts of cases of active tuberculosis, either carrying out the examination himself or urging those under his care to cooperate with the public health workers in such an examination. If treatment of a contact is advised, he may be asked about the wisdom of such treatment or in some cases he may be asked to supervise the treatment. In either circumstance, the regularity of application and the completion of the recommended term of treatment are likely to depend on the attitude of the personal physician.

His attitude will also determine the thoroughness of the examination of persons found to have abnormalities on x-ray examination of the chest, whether such an examination was initiated individually by him or whether it was a part of a group examination with the reports of abnormality sent to the personal physicians. These roentgenographic abnormalities should be evaluated carefully as they may present the golden opportunity to diagnose tuberculosis or some other serious pulmonary disease. The wise physician will not be misled by the absence of symptoms or a negative result from physical examination.

If such an investigation leads to a diagnosis of inactive tuberculosis, the personal physician should urge the patient to return for regular follow-up examinations so that any change in the dynamic status of the disease will be detected with as little delay as is practical. Most patients appreciate the physician's display of such interest in their welfare.

Many of the case-finding activities are carried out by official agencies such as public health departments or school medical departments. Even in this situation the personal physician can be useful by urging his patients to cooperate wholeheartedly in such organized efforts to find all cases of tuberculosis and tuberculous infection so that we can move steadily toward the goal of eradication of the disease.

Program evaluation is the responsibility of the constituents and affiliates of the National Tuberculosis Association and the official health agencies. Even in this aspect of the program for the eradication of tuber-

culosis there is a place for the physician. He can participate in the activities of the tuberculosis association, and as a citizen he should be sure that his community has an optimal public health department. Such a department is necessary if we are to achieve the goal of eradicating tuberculosis. As pointed out in the Appendix, all necessary anti-tuberculosis services should be available to all people, regardless of their legal residence or their ability to pay for such services. As tuberculosis is most common among the less privileged among us, adequate public medical care must be provided for many if we are to stop the spread of the infection.

Tuberculosis should be considered a disease of the community manifested in certain individuals within the community. As the disease is of the community, it is the responsibility of the community to eradicate the infection from its midst. It is truly a heroic task, and America's personal physicians have a heroic mission in this battle.

APPENDIX: TUBERCULOSIS ERADICATION PROGRAM³

The National Tuberculosis Association Committee for the Guidance of the Tuberculosis Program believes that the following program activities are basic aspects of a tuberculosis eradication program for the United States today applicable to all communities. These activities are divided into three categories which are absolutely necessary in any tuberculosis eradication program:

Treatment

Case Finding

Program Evaluation

These categories are of equal importance, but in each category the activities listed below are in order of priority.

The services listed should be available to all people regardless of their legal residence or their ability to pay.

Treatment

A. Adequate treatment of all known patients with active tuberculosis.

This will require at least:

1. Adequate medical and paramedical personnel; adequate hospital, clinic, and laboratory facilities; and provision of all necessary drugs.
2. Lifetime follow-up after completion of treatment.

Case Finding

- A. Prompt examination of the contacts of all cases of active tuberculosis with appropriate treatment of such contacts when indicated, and adequate follow-up of all contacts.
- B. Prompt and thorough examination of persons found to have abnormalities on x-ray examination of the chest, and of persons suspected to have tuberculosis in other parts of the body.
- C. Lifetime follow-up of persons with inactive tuberculosis.

- D. Examination of those groups of people which are known to have a high prevalence of tuberculosis, especially those likely to infect others.
- E. Identification of persons most likely to infect children. This will require at least:
 - 1. Periodic examination of teachers, other school employees and all other individuals who are in regular close contact with children.
 - 2. Tuberculin testing all school enterers and examination of the close contacts of those found to react.
- F. Motivation of individuals to accept personal responsibility for the detection of tuberculosis by:
 - 1. Tuberculin testing 7th graders and carrying out an intensive health education program to motivate the reactors to obtain annual chest x-rays for the rest of their lives.
 - 2. An educational program to persuade all people to have an annual medical check-up to include appropriate tests for tuberculosis.

Program Evaluation

- A. Use of *Goals and Standards for Eliminating Tuberculosis** in evaluating the adequacy of the program.
- B. Periodic tuberculin testing of a statistically determined representative sample of the population, not for the primary purpose of case finding, but (1) to serve as an epidemiologic index of infection in the community; (2) to detect areas of unusually high prevalence of infection requiring intensive investigation and control; and (3) to estimate progress in the reduction of tuberculous infection.

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Farmer's Lung and Silo-Filler's Disease

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When compared to brucellosis and accidents with farm machinery, farmer's lung and silo-filler's disease—and especially the latter—are relatively uncommon occupational hazards. Even so, each of these conditions constitutes a definite farm medical problem. Because both occur most frequently in farmers and involve the lung, they frequently are confused. Clinically they show many similarities in the acute phase, and an attack of farmer's lung may be precipitated by working in a silo; but the differences in cause and pathogenesis are great. A simple clinical history of the nature of the exposure is all that is required to distinguish between these conditions.

FARMER'S LUNG

Farmer's lung is a granulomatous interstitial pneumonitis which occurs in sensitized individuals on exposure to moldy forage. Clinically, the acute phase of this disease is of primary interest, but the chronic phase resulting from repeated exposures is also recognized as one of the conditions producing chronic pulmonary fibrosis and pulmonary insufficiency. The condition was first reported by Campbell in 1932 from Westmorland, England. Subsequently it has been reported from the United States, Switzerland, Iceland, Norway, Sweden, and Finland. Clinical observation has supplied adequate proof that farmer's lung is a distinct entity. In 1958, Dickie and Rankin and Totten and associates described its pathogenesis as their experiences with lung biopsy suggested; and in 1961 Pepys confirmed the allergic origin of the disease by demonstration of precipitins against antigens from moldy hay in the serum of patients with farmer's lung.

The acute phase of farmer's lung is a respiratory illness lasting three to seven days, in individuals previously sensitized upon exposure to moldy forage produce. Specifically, the material may be hay, grain, silage, tobacco, or threshing and shredding dusts. Most of the patients are farmers, but occasionally individuals of other occupations are affected. The condition

occurs in both men and women. The youngest patient observed by Dickie and Rankin was a 12-year-old boy.

Exposure to dust is followed in six to eight hours by chills, fever, cough, and dyspnea. Dyspnea occurs in all, and in some patients is accompanied by cyanosis. Although the chills and fever subside in three to seven days, the dyspnea persists for several days to weeks after an attack. Patients who also suffer from asthma can distinguish this acute dyspnea from an asthmatic attack. The breathing is shallow and rapid, with difficult inspiration being the most prominent feature. Crepitant rales and rhonchi may be evident on auscultation but there are no signs of consolidation. The wheezing and obvious expiratory effort of the asthmatic are absent.

The reversal of the tuberculin reaction was first noted by Törnell in 1946. According to Fuller, a positive Mantoux reaction during the active phase of the disease renders a diagnosis of farmer's lung doubtful.

Chest roentgenograms show diffuse interstitial pneumonitis with patchy pneumonic densities. These densities gradually change from a diffuse ground-glass appearance to a finely reticular pattern, and eventually clear if there are no subsequent attacks over a period of a few months.

The pathologic features of the acute phase have been established by lung biopsy. The histologic pattern is that of a granulomatous reaction with nodules of poorly defined epithelioid cells and tubercle formation. Occasional scattered giant cells of Langhan's type are present but caseation necrosis is not. The alveolar septa are involved and are swollen with collections of lymphocytes and plasma cells. At a later phase, biopsy reveals no acute granulomatous reaction but diffuse interstitial fibrosis in alveolar walls and septa. There are no giant or epithelioid cells at a late stage. Studies of pulmonary function indicate that the lung tissue is stiff, resistant, and moderately hyperinflated and that the alveolar capillary membrane is thickened. These changes cause a reduction of lung volume and maximal breathing capacity and an impairment of alveolar capillary diffusion which lead to hypoxia. The duration of the granulomatous reaction is unknown, but the return to normal of the findings from pulmonary-function studies and the exercise tolerance suggests that the lesion is a reversible one and does not lead to a significant degree of interstitial fibrosis unless multiple attacks occur.

Treatment consists in the complete avoidance of exposure to moldy forage dusts. Farmers who have demonstrated sensitivity to these products should not enter barns, silos, or other enclosures which contain these dusts; and if exposed in the open, they should be protected with adequate masks. For young persons a change of occupation is desirable. After exposure has occurred and the acute phase has developed, and for patients who cannot entirely avoid exposure, steroids may be beneficial in suppressing tissue sensitivity.

SILO-FILLER'S DISEASE

Silo-filler's disease results from exposure to the toxic gas, nitrogen dioxide. This gas is capable of producing a chemical burn of the tracheo-bronchial tree and sometimes causes death. Nitrogen dioxide forms in silos freshly filled with either corn or alfalfa.

Our first experience with this syndrome occurred in 1955, when two farmers were registered at the Mayo Clinic after becoming ill while filling silos.³ One man had been treated at home for several days with oxytetracycline (Terramycin), but had become worse and therefore was transferred to St. Marys Hospital in Rochester. He was cyanotic and dyspneic and appeared to be in an extremely toxic state. The rectal temperature was 105°F. A thoracic roentgenogram made with a portable apparatus, although technically unsatisfactory, showed what was interpreted as bilateral pneumonitis (Fig. 1). Penicillin and oxygen were administered, but the patient died two hours after admission to the hospital. Necropsy revealed extensive congestion and edema in the lungs (Fig. 2, *a*). Histologic examination disclosed marked pulmonary edema and congestion with early exudation of neutrophils into the alveolar spaces (Fig. 2, *b*). Some alveolar septa were thickened by cellular infiltrate.

The second farmer had become ill while putting newly chopped corn silage into a silo. He had noticed "acid-like" fumes in the form of a thin haze in the silo. After the ensiling was finished, he had experienced the sensation of constriction about the thorax, associated with shortness of breath and cough. His home physician had prescribed antibiotics, and a week in bed had brought considerable improvement. About a month after the onset of illness he had begun to experience shaking chills, fever, anorexia,

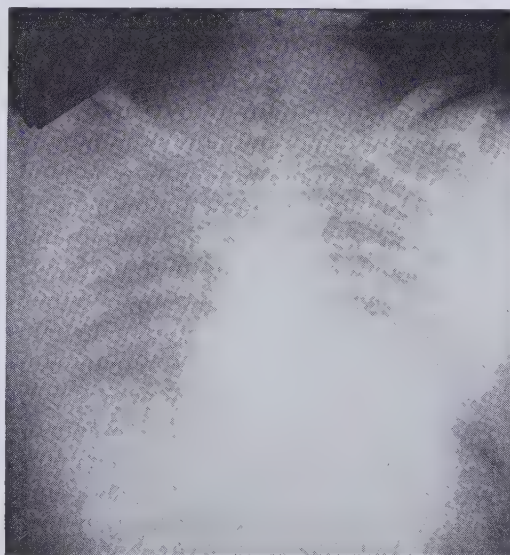


Figure 1 (First case). Roentgenogram made with portable apparatus, showing bilateral infiltration.

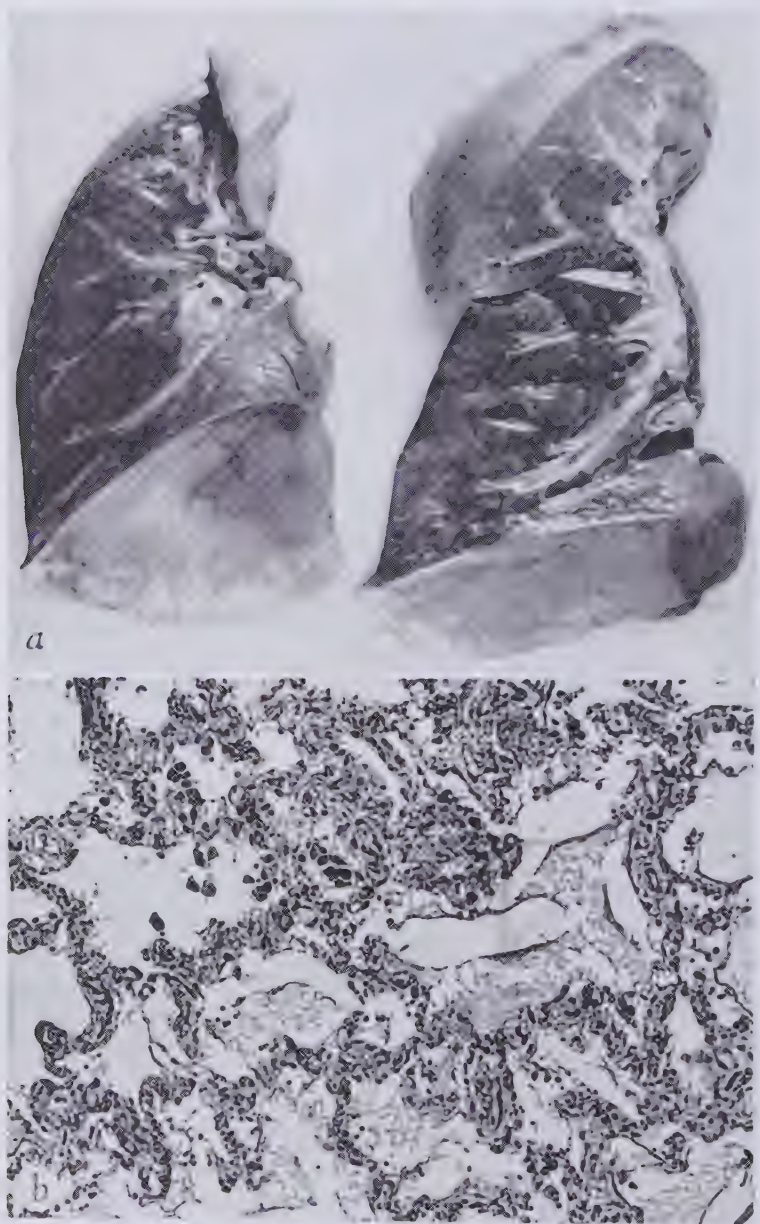


Figure 2 (First case). *a*, Gross specimen, showing extensive congestion and edema. *b*, Congestion and pulmonary edema with signs of early bronchopneumonia (hematoxylin and eosin; $\times 150$).

increased cough, and a pressure-like pain in the thorax, and bloody sputum was noticed. He had been referred to the Mayo Clinic.

On admission to the hospital the temperature was 102° F. The chest roentgenogram (Fig. 3, *a*) showed extensive, bilateral, diffuse infiltration mainly involving the upper halves of both lung fields. With rest in bed as the only treatment, this patient recovered. The findings from pulmonary-function tests and thoracic roentgenography (Fig. 3, *b*) were normal.

In an attempt to find the cause of this condition, inquiries were made of various farm schools in the Midwest. Professor W. H. Peterson and his associates at the University of Wisconsin⁷ had written in *Hoard's Dairyman* for December, 1949, that nitrogen dioxide would form in lethal concentrations during the filling of silos with corn forage. Their studies had been initiated by reports from farmers in the preceding 10 years that a yellow-brown gas appeared in and just outside of the silo in the first four or five days after filling of the silo. On some occasions this had been considered the cause of death of chickens and other small animals in the vicinity of the silo. It was found that nitrogen dioxide would reach concentrations of 151 parts per million in the connecting silo room after recent filling of the silo. Concentrations greater than 10 to 25 parts per million have been thought unsafe to breathe.

Clinically, silo-filler's disease is characterized by two relatively acute periods of illness separated by a period of two to four weeks during which the major symptoms relent. The initial acute phase follows exposure to nitrous dioxide. In all cases reported the patients had entered a silo which had been filled with fresh chopped corn or alfalfa one to three days prior to entry, and all were aware of cough, dyspnea, weakness, and a sensation of choking while in the silo. These symptoms improve but the cough,

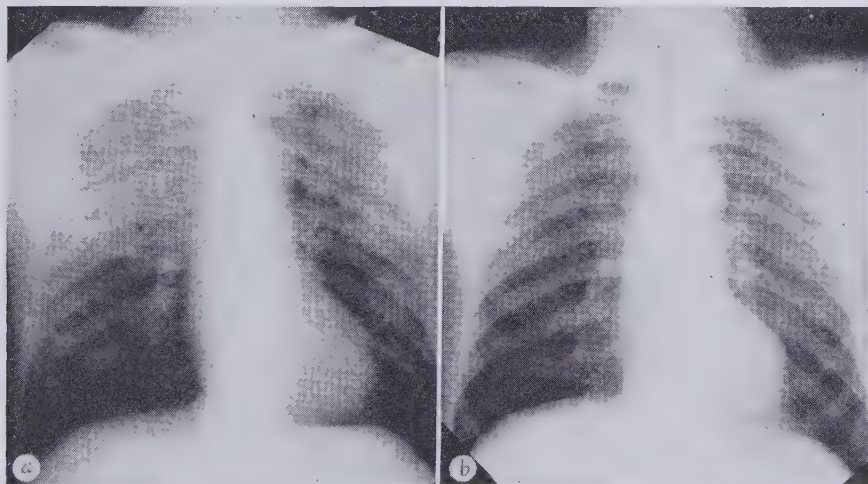


Figure 3 (Second case). *a*, Extensive, bilateral, diffuse mottling on admission. *b*, Clearing of previous process, as demonstrated two weeks after dismissal from hospital.

dyspnea, and weakness never completely disappear during the following period of quiescence.

The second acute phase of the illness is marked by the onset of fever, chills, malaise, and a decided increase in the cough and dyspnea. The sputum may be bloody. Tachypnea and tachycardia are always present. On auscultation, numerous moist inspiratory rales and expiratory rhonchi are present over both lungs. The chest roentgenogram shows extensive diffuse miliary mottling. The most significant hematologic finding is neutrophilic leukocytosis and a gradual increase in carbon-dioxide retention. Death may occur very soon or within three weeks to a month from the date of the initial exposure, or recovery may be achieved gradually over a period of one to two months from the time of the second acute phase.

Pulmonary-function studies in one case indicated no residual impairment of function one month after the second phase. The pathologic changes are limited to the lungs and are dependent upon the duration of life after exposure. In patients who die in the early phase, there is marked edema and exudation into the alveolar spaces and thickening of the alveolar walls with lymphocytic cellular infiltrates. In those who die in later phases, there is destruction of the bronchiolar walls and plugging of the bronchioles with an organizing fibrous exudate producing bronchiolitis obliterans. Similar lesions are known to be produced by exposure to phosgene, ammonia, chlorine, chloropicrin, and other irritant gases.

Treatment and Prevention

During the acute phases of the disease, treatment is directed toward relief of pulmonary edema and the effects of secondary infection. Oxygen must be supplied if the dyspnea is severe, and positive-pressure breathing may be required. Broadly effective antibiotics are advisable, as well as steroids in large doses to suppress the fibrotic reaction that occurs late in the disease.

The measures of best effect are, of course, those which prevent. Rodney A. Briggs of the University of Minnesota Experimental Station formulated in 1959 a set of precautions for avoiding silage-gas poisoning. They are:

1. During silo filling, watch for irritating yellow or brown fumes in or near the silo. If you see such fumes, get away and stay away from the silo. The poisonous gases—nitrogen dioxide or one of the other oxides of nitrogen—are heavier than air and tend to settle downward and hover around the base of the silo.
2. Let no one enter the silo without first running the blower for 10 to 15 minutes to ventilate completely the silo, chute, and silo room. It is wise to do this during filling, and whenever anyone enters the silo during the 10 days after filling.
3. Leave the chute door open at the top surface of the silage. This will prevent gases from accumulating at the top of the silage.

4. Provide extra ventilation at the base of the chute when the silo is attached to the barn. If you have a separate silage room, it is wise to make an outside door for this room, and leave it open during and after filling so that gas can escape at the floor level.

5. Keep children and animals away from the silo for 10 days after filling.

We are indeed indebted to the members of the University of Wisconsin Farm School for first calling attention to the hazard of silo-filling, as well as for the conducting of experiments which identified the specific toxic gas that was involved.

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Recent Advances in the Diagnosis of Bronchogenic Carcinoma

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Bronchogenic carcinoma presents a great and growing problem. It is by far the most common type of cancer encountered in men, currently causing as many deaths each year as do automobile accidents.² Unfortunately, the results of treatment for bronchogenic carcinoma are not much better today than they were almost a generation ago. During the years 1943 to 1949 the five-year survival rate of patients with lung cancer who were seen at the Mayo Clinic was about 9 per cent.¹⁵ In the period from 1950 to 1957 the survival rate rose only slightly, to 14 per cent.¹⁰

At the present time, surgery offers the only hope of cure for lung cancer and there is no consistently effective form of palliation. Yet about half of all patients with bronchogenic carcinoma have tumors that are already inoperable by the time the diagnosis is established. Until more effective therapy becomes available, any improvement in this grim outlook will necessarily have to come either from earlier diagnosis or from preventive measures.

Preventive measures—and particularly those aimed at reducing cigarette smoking and atmospheric pollution—have received considerable attention lately.² Such measures are important and should be encouraged, but they are beyond the scope of this discussion.

Attempts to detect bronchogenic carcinoma in its early stages can be very frustrating. The tumor may be completely asymptomatic, or it may masquerade as pneumonitis or some other nonmalignant pulmonary or systemic disease process. Standard diagnostic procedures such as routine thoracic roentgenography, examination of spontaneously expectorated sputum for cancer cells, and bronchoscopy may give negative or indeterminate or unsatisfactory results; and in consequence thoracotomy may be delayed and the chance for a cure lost.

Completely reliable techniques for establishing a diagnosis of bronchogenic carcinoma are not available now. However, the past few years have witnessed the introduction of many new diagnostic aids, including certain clinical clues as well as various roentgenographic, cytologic, bronchoscopic, and biopsy procedures. The purpose of this discussion is to review some of these diagnostic aids, with emphasis on techniques for inducing formation of sputum and procedures involving use of hematoporphyrin derivatives.

CLINICAL CLUES

Bronchogenic carcinoma is most likely to occur in men past 45 years of age who are chronic heavy smokers of cigarettes and live in urban areas where there is concentrated air pollution. Anyone in this high-risk group deserves close observation and is a candidate for periodic screening by radiologic and cytologic studies. Carcinoma should be strongly suspected whenever such a person develops localized pulmonary symptoms or infection, particularly pneumonitis of the segmental, excavating, or recurrent type.³⁷

Recently attention has been focused upon a number of extrathoracic signs and symptoms that may occur in association with bronchogenic carcinoma. Skeletal, cutaneous, neurologic, cardiovascular, hematologic, and metabolic syndromes have been described.¹⁷ These are presented in detail in another article in this volume (see page 921). When one of these symptom complexes develops, bronchogenic carcinoma should be considered, especially if the patient belongs to the high-risk group and if the symptoms develop abruptly and progress rapidly.

ROENTGENOGRAPHIC PROCEDURES

Study of the standard thoracic roentgenogram remains the single best screening procedure for bronchogenic carcinoma. Community-wide radiologic surveys of the type that identify cases of tuberculosis by mass methods have given disappointing results when applied to the problem of early detection of lung cancer. However, radiologic surveys might be worthwhile in the study of selected high-risk groups of men over 45 years old who are urban dwellers or heavy cigarette smokers.³⁷

The value of roentgenographic techniques, notably laminography, in the study of solitary pulmonary nodules has been commented upon by Good. Cancer can be reasonably excluded if it can be demonstrated conclusively that a solitary nodule contains calcium.

There are some enthusiastic advocates of bronchography as a method for distinguishing purely inflammatory pulmonary disease from carcinoma with associated bronchial obstruction.³⁸ Our own experience with this

application of bronchography has been rather limited, possibly because we have been reluctant to place great reliance upon it. Nevertheless, we have found bronchograms helpful in selected cases—for example, when bronchiectasis has been demonstrated plainly in a contracted segment or lobe of lung where cancer had been feared.

Routine fluoroscopy and the newer amplified-image fluoroscopy may sometimes help elucidate the nature of an abnormal hilar or mediastinal shadow. It has been demonstrated repeatedly, however, that these techniques cannot always be depended upon to distinguish vascular abnormalities from tumors or enlarged lymph nodes. Angiocardiography is considerably more discriminating in this regard,⁵ but even this procedure is subject to errors of interpretation.

CYTOLOGIC METHODS

Studies of sputum and bronchial washings for cancer cells, when properly performed, are extremely valuable in the diagnosis of bronchogenic carcinoma. In fact, no other test in current use has a greater degree of diagnostic accuracy, except for thoracotomy and open-lung biopsy.³⁰ Roentgenographic procedures may be more sensitive as screening devices, but they are not diagnostic and require histologic or cytologic confirmation.

Published data indicate that cytologic findings are positive for cancer cells in about 70 per cent of cases of bronchogenic carcinoma (range: 40 per cent to 90 per cent).³⁰ Optimal diagnostic accuracy is achieved when multiple specimens of sputum are carefully collected, processed, and screened by well-trained, conscientious technicians.

Recently a number of procedures have been suggested for concentrating cancer cells in the sputum specimen and for facilitating their identification. Proposed methods for concentration include membrane filtration⁷ and treatment of the sputum with mucolytic agents such as N-acetyl-L-cysteine (Acetylcysteine)¹⁹ or with enzymes such as pancreatin, trypsin, chymotrypsin, and hyaluronidase.^{8, 18} Procedures for improving identification of cancer cells utilize special stains or fluorescence techniques.²⁷

Of course not everyone with lung cancer expectorates cancer cells. If the tumor does not communicate with a bronchus (for example, a small peripheral cancer), or if bronchial obstruction is present, cancer cells may not reach the trachea. Conversely, cancer cells may be able to reach the trachea but the patient may not produce enough bronchial secretion to expectorate them. In this latter situation procedures designed to induce the formation of sputum have been employed.

Most methods now used for inducing sputum involve the inhalation of heated aerosolized solutions containing saline, propylene glycol, or glycerine in various concentrations.^{4, 13, 14, 23, 35} A technique utilizing an

aerosolized solution of sulfur dioxide was also available at one time, but equipment for its use is no longer manufactured.¹

At our clinic, formation of sputum is induced by having the patient inhale an aerosolized solution of 15 per cent saline and 20 per cent propylene glycol, preheated to 160° F.⁹ The period of inhalation is approximately 15 minutes. If the patient has asthma or severe emphysema the saline concentration is reduced to 3 to 5 per cent, in order to decrease the risk of bronchospasm. Concern over possible exposure of laboratory personnel to tuberculosis or other contagious diseases has led to development of protective devices to shield the patient's face when he coughs and to remove expectorated sputum droplets from the air.³⁶

We now have used techniques for inducing sputum in more than 1000 cases and have obtained a satisfactory specimen of sputum in almost 99 per cent. Adverse reactions have occurred rarely, the only kind of any consequence being bronchospasm caused by the inadvertent use of 15 per cent saline solution in asthmatics or severe bronchitics.

It has been our practice to collect one sputum specimen directly following the induction procedure and another during the ensuing 24 hours. Examination of both of these specimens provides a greater degree of diagnostic accuracy than examination of either one alone.⁹ False-positive reports of cancer cells in specimens of induced sputum are exceedingly rare in our experience.

We have found methods for inducing sputum to be of considerable value in diagnosis of lung cancer, both among patients who cannot raise sputum spontaneously and among those who can. Our data indicate that among patients who cannot raise sputum spontaneously, cytologic studies of induced sputum have a diagnostic accuracy comparable to that of conventional cytologic techniques for sputum among patients who do expectorate. Further, regarding this latter group we have evidence that induction methods may enhance the diagnostic accuracy of conventional cytologic studies of the sputum. In a number of cases it has been possible to demonstrate cancer cells in preparations of induced sputum after studies of apparently satisfactory specimens of spontaneously expectorated sputum were negative.

As is the case with all cytologic techniques for sputum,³⁴ studies of induced sputum give their best results with large primary bronchogenic cancers that involve major bronchi. Results in general are poorer with cancers that are metastatic to the lung, small, or peripheral. Even with tumors of this sort, however, where one would anticipate a relatively low diagnostic yield, the results of induced-sputum studies have been rather impressive. In selected cases, a specimen of induced sputum that was positive for cancer cells has provided a definitive diagnosis and obviated the need for further diagnostic study.⁹

Cytologic studies are now used extensively as screening procedures for the detection of in situ cancer of the uterus. Similarly, cytologic

studies of sputum—and particularly induced sputum—may eventually prove highly useful in surveys designed to detect bronchogenic carcinoma in its early stages.²⁰ Indiscriminate, large-scale cytologic surveys of sputum do not seem practical at the moment; but periodic screening of selected high-risk populations might be rewarding.^{21, 37}

BRONCHOSCOPIC PROCEDURES

That various chemical substances tend to accumulate in malignant tissue has long been known. Hematoporphyrins, tetracycline, and more recently demethylchlortetracycline (Declomycin) have been identified with this behavior. Their presence can be detected readily by the demonstration of fluorescence in the tumor. The importance of any technique that will demonstrate the presence of malignant tissue in the body is obvious.

Lipson and his associates²⁴ prepared an acetic acid-sulfuric acid derivative of hematoporphyrin and were able to demonstrate that this substance localized in malignant tumors of animals. In order to activate the red fluorescence that indicated the presence of the hematoporphyrin derivative, it was necessary to illuminate the tumor with a suitable light. Satisfactory visualization was obtained by using a 200-watt high-pressure mercury lamp fitted with a Schott filter (wavelengths about 400 millimicrons). The tumor was examined through a Corning filter that transmitted only red light resulting from the fluorescence. In the experimental work with animals it was demonstrated that maximal fluorescence took place about three hours after intravenous injection of the hematoporphyrin derivative. It was of particular interest that the most marked fluorescence was observed at the periphery or advancing borders of the tumor.

Following the experimental work, the technique was applied to the detection of malignant tumors in human beings, and specifically to the endoscopic demonstration of malignant lesions of the tracheobronchial tree and the esophagus. The hematoporphyrin derivative was administered intravenously in a dose of 1.5 to 2 mg./kg. body weight about three hours prior to endoscopic examination. Illumination was accomplished by transmitting the activating light from the mercury lamp to the tip of the bronchoscope or esophagoscope via a fiber-glass cable and a quartz rod.²⁵ The area to be examined was viewed through a Corning filter that transmitted only the red fluorescent light.

At our institution the hematoporphyrin method has been used in a series of 50 cases.²⁶ In 20, a diagnosis of bronchogenic carcinoma eventually was proved; and in nearly all of these, adequate fluorescence was demonstrated. In some cases localization of the fluorescence indicated the best site for biopsy. The thorax of one patient appeared normal roentgenographically, but bronchogenic carcinoma was suspected because of the presence of malignant cells in the sputum. A careful examination of the

bronchial tree with the standard bronchoscope and available telescopes failed to reveal the source of the tumor cells. A second examination was performed with the modified bronchoscope after administration of the hematoporphyrin derivative. Fluorescence was noted in the bronchial orifice of the right upper lobe, and a biopsy from this region disclosed bronchogenic carcinoma. In another patient, who had a bronchogenic carcinoma involving the right main bronchus, the area of fluorescence extended up into the trachea and involved the bifurcation. Because there was no gross evidence of extension above the right main bronchus, surgical treatment was attempted; but at operation it was demonstrated that the tumor did involve the trachea and mediastinal structures and was truly inoperable.

Also, bronchoscopy was performed in several patients with carcinoma of the mid-esophagus after administration of hematoporphyrin, to see whether fluorescence could be detected in the posterior wall of the trachea. In at least two instances fluorescence was noted beneath the tracheal mucosa, suggesting that the esophageal cancer was invading the trachea and was therefore inoperable.

Although present methods of detecting bronchogenic carcinoma by standard bronchoscopic techniques are generally satisfactory, it is evident that the use of hematoporphyrin and fluorescent lighting may be very helpful in certain cases. We must point out, however, that patients who are given hematoporphyrin derivative should be cautioned not to expose themselves to bright sunlight for at least two days. The only adverse effects we have noted with this procedure have been related to the phenomenon of photosensitivity. A limitation of the procedure is our inability as yet to obtain adequate visualization of fluorescence within the upper lobes or other areas of the bronchial tree normally viewed with the right-angle telescope.

It has been mentioned that adaptation of the bronchoscope for fluorescent lighting was accomplished by substituting a quartz rod for the conventional distal light carrier and by using a short fiber-glass cable to transmit the light from its source to the quartz rod.²⁵ Although this modification was designed specifically to conduct the activating blue-violet light used in hematoporphyrin procedures, we have found it exceptionally good also for the transmission of ordinary white light. Superior visualization of all the parts of the bronchial tree can be obtained with the modified instrument. The use of quartz rods in bronchoscopes is not new, but most of their employment has been in endoscopic photography. It seems likely that fiber-glass units may replace our present lighting systems in all types of endoscopes in the future. With the aid of fiber-glass cables we should be able to visualize better the upper lobes and other relatively inaccessible parts of the bronchial tree.

In addition to the usual methods for obtaining a bronchoscopic biopsy, there are two special procedures that might be mentioned. Andersen

has used a transbronchoscopic, so-called lung biopsy technique to establish a diagnosis of diffuse pulmonary carcinomatosis when the finding from routine bronchoscopic examination was negative. The technique entails blind biopsy sampling of a small peripheral bronchus located in the area of most extensive disease as judged by the thoracic roentgenogram.

It is also possible to perform needle biopsy of peribronchial tumors or enlarged lymph nodes at the hilus or tracheal bifurcation via the bronchoscope. Several types of biopsy needles have been designed for this purpose. One of us (A.M.O.) has successfully biopsied an extrabronchial carcinoma using the Vim-Biegeleisen needle after multiple specimens obtained with the standard bronchoscopic biopsy forceps had been negative.

BIOPSY PROCEDURES

Biopsies at bronchoscopy or thoracotomy are standard procedures for establishing a diagnosis of bronchogenic carcinoma and for determining operability. Transbronchoscopic needle biopsy and biopsy of small peripheral bronchi have been considered already, but there are a number of other biopsy techniques that may aid in the diagnosis of lung cancer.

Scalene lymph-node biopsy can furnish evidence of inoperability simultaneously with definitive diagnosis.^{29, 32} This procedure is indicated whenever enlarged lymph nodes can be palpated in the supraclavicular area. It is of questionable value in cases of cancer without palpable nodes, although it might be considered in the presence of hilar or peritracheal tumors or nodal enlargement.

Various procedures have been developed which permit visualization and biopsy of upper mediastinal lymph nodes and tissue through a small cervical incision.^{6, 12, 33} These techniques utilize blunt dissection and either a conventional laryngoscope or a specially designed "mediastinoscope," such as the one devised by Carlens. Proponents have found them safe and helpful in diagnosing and estimating chances for surgical cure of bronchogenic cancer. The techniques have not been widely accepted, however, because of concern over the risk of damage to important mediastinal structures.

Needle biopsy is a relatively simple method for diagnosis of large peripheral lung tumors or tumors involving the pleura, ribs, or chest wall,^{22, 31} but this kind of biopsy should be reserved for presumably inoperable lesions because of the danger of seeding cancer cells along the needle tract.³⁷ Other hazards include bleeding, pneumothorax, and bronchopleural fistula.

McGoon has described recently an ingenious procedure for biopsy of carcinoma involving the superior pulmonary sulcus (Pancoast tumor). A transcervical approach is used and the specimen is taken by either needle or incisional means under direct vision.

So-called limited thoracotomy, using a short incision, may provide adequate exposure for biopsy of diffuse and obviously inoperable cancer.¹⁶

SUMMARY

Early diagnosis is essential in order to obtain optimal results in the treatment of bronchogenic carcinoma. One should be aware of the insidious nature of the disease and its tendency to affect men over 45 years old who smoke many cigarettes. These high-risk patients need careful study if they develop localized respiratory symptoms or infections, and might benefit from periodic screening with thoracic roentgenograms and cytologic studies of sputum.

Extrathoracic manifestations may be significant diagnostically.

The standard thoracic roentgenogram is the most sensitive test for bronchogenic cancer, but it is not diagnostic. Other useful radiologic procedures are laminography, bronchography, fluoroscopy, and angiocardiology.

Among the more specific tests for bronchogenic carcinoma, cytologic studies of sputum have the greatest diagnostic accuracy of all procedures except lung biopsy. The diagnostic accuracy of cytologic studies can be increased by the application of techniques for inducing formation of sputum.

New and promising in the endoscopic field are procedures that utilize hematoporphyrin. This substance shows a predilection for malignant tissue and exhibits fluorescence when exposed to a specific activating light. Hematoporphyrin techniques have made possible the optical diagnosis of lung cancer prior to histologic confirmation.

Transbronchoscopic needle biopsy and so-called blind biopsy of small peripheral bronchi have each been helpful in selected cases of bronchogenic carcinoma. Other biopsy techniques that have diagnostic or prognostic value include scalene or mediastinal lymph-node biopsy, transcervical biopsy of superior sulcus tumors, and needle or incisional biopsy of the lung.

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Extrathoracic Manifestations of Bronchogenic Carcinoma

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Bronchogenic carcinoma has increased in incidence to an alarming degree, and the results of treatment have left little room for complacency among physicians. Earlier diagnosis would be an obvious improvement for the unfortunate patients. The symptoms most commonly associated with such a lesion are pulmonary, such as cough and hemoptysis; but there are extrathoracic manifestations not due to metastasis which may indicate the presence of these malignant pulmonary neoplasms. Familiarity with these manifestations can lead to earlier diagnosis of the cancer and possibly to an improvement in the survival rate.

These abnormalities cannot be accurately and rigidly classified, but most can be included in six systems: skeletal, cutaneous, neurologic, cardiovascular, hematologic, and metabolic. Manifestations caused by metastasis or by mechanical effects of the tumor (such as obstruction of the superior vena cava, compression of the brachial plexus, or dysphagia due to esophageal compression) will not be included.

SKELETAL MANIFESTATIONS

Digital Clubbing and Pulmonary Hypertrophic Osteoarthropathy

Clubbing associated with neoplasms is slightly different from that associated with chronic pulmonary insufficiency. When due to a neoplasm, clubbing is often painful, develops rapidly, and appears acute because of a red rim in the skin immediately surrounding the base of the nail. There is actually a measurable increase in the peripheral blood flow in this type of clubbing (Holling and associates). Pulmonary hypertrophic osteoarthropathy is manifested by painful periosteal proliferation in the long bones, arthralgia, and joint swelling which occasionally resembles rheumatoid

arthritis. Clubbing usually appears before osteoarthropathy, but occasionally the reverse is true and they do not necessarily occur together.

These two are probably the most frequent peripheral manifestations of bronchogenic carcinoma, occurring in 5.2 per cent of 481 cases with pulmonary resection reviewed by Wierman and co-workers, and in 12 of 100 consecutive cases of bronchogenic carcinoma examined by Hansen. Clubbing and osteoarthropathy may be more severe when pulmonary suppurative disease is associated with the carcinoma, but according to Knowles and Smith they are more frequent with tumors located in the periphery of the lung and those having central necrosis. Although any histologic type of bronchogenic carcinoma may be found, the squamous-cell variety is the most common.

The pathogenesis of clubbing and pulmonary osteoarthropathy is not known for certain, but Holling and his associates have shed considerable light on the problem. It has long been observed that many patients are free of pain upon waking from surgical resection of the tumor. Holling noted that the bounding peripheral pulsation and increased peripheral blood flow also decreased postoperatively, and further that this change occurred exactly at the time of severance of the lung pedicle or of ligation of the bronchus—not when the pulmonary vessels were severed. This evidence favored neurogenic rather than humoral etiology, so the investigators studied dogs with pulmonary tumors and hypertrophic pulmonary osteoarthropathy. Cross-circulation between such a dog and a normal dog did not produce osteoarthropathy in the normal animal. After cutting of the vagus nerve in the neck, however, on the same side as the pulmonary lesion, the peripheral blood flow decreased and the osteoarthropathy disappeared. The afferent pathway of this mechanism, therefore, is neurogenic and by way of the vagus nerve. The efferent pathway is still unknown. Diner has reported clinical confirmation of this work in one case, where vagotomy proximal to the hilum produced relief of hypertrophic osteoarthropathy without resection of the lung or tumor itself.

CUTANEOUS MANIFESTATIONS

Dermatomyositis

At the Mayo Clinic 15 per cent of all adults with dermatomyositis have a carcinoma somewhere. This proportion is even higher among those who develop dermatomyositis after the age of 40. Arundell and his co-workers found that 12 (52 per cent) of their 23 patients over 40 years of age with dermatomyositis had carcinoma, and some had bronchogenic cancers.

Dermatomyositis is a combination of polymyositis and cutaneous lesions. Muscular tenderness, weakness, and atrophy may be confined to

small groups of muscles, as in the shoulders; or muscles of the entire body may be involved. Cutaneous lesions are inconstant and variable; but they usually are erythematous and edematous, sometimes violaceous.

Dermatomyositis usually appears before discovery of the carcinoma, and its onset after the age of 40 should start the physician on a thorough search for an occult cancer. Remissions of the disease have occurred frequently with treatment of the primary tumor.

Acanthosis Nigricans

Patients more than 40 years old who develop acanthosis nigricans invariably have a visceral malignant tumor. The cutaneous lesion, darkly pigmented and rather verrucous, occurs in body folds or sometimes on mucous membrane. The cancer usually is an intra-abdominal adenocarcinoma, but sometimes may be primary in the lung or breast. The cutaneous changes regress with removal of the tumor and return with the development of metastasis.

NEUROLOGIC MANIFESTATIONS

Myasthenic Syndrome

In 1953 Anderson and co-authors first recognized the myasthenia-like syndrome in a patient with a bronchogenic carcinoma who had prolonged apnea after administration of succinylcholine during operation. In 1960 Rooke and his co-workers described the syndrome in considerable detail as they had observed it in 19 patients. Myasthenia was the first symptom in all cases, and bronchogenic carcinoma was not recognizable in some until several months after weakness had first been noted. Almost always the carcinoma was of the small-cell variety.

These authors noted several characteristics of the myasthenic syndrome associated with the small-cell type of bronchogenic carcinoma which were different from those of myasthenia gravis. In the myasthenic syndrome there was weakness of the proximal muscles, particularly those of the pelvic girdle; and this was uncommon in myasthenia gravis. Furthermore, the bulbar and ocular muscles usually were not involved in the myasthenic syndrome, but in myasthenia gravis such involvement was common.

Perhaps the most distinctive characteristic of the myasthenic syndrome is the temporary increase in muscular strength after a few seconds of voluntary exercise, whereas the reverse is true in myasthenia gravis. The electromyographic findings demonstrate this beautifully and seem to be quite specific: the action potential is reduced in the resting muscle after a single stimulus, but increases after a few seconds of exercise or stimulation. In myasthenia gravis the action potential of resting muscle is normal and decreases with further stimulation.

The exact pathogenesis of this syndrome remains obscure. Electrolytic disturbances have been implicated but rejected after investigation. Treatment of the primary tumor has effected improvement in muscular strength and in the electromyogram.

Peripheral Neuropathy

Bronchogenic carcinoma is the most common cause of carcinomatous neuropathy.⁶ This syndrome is manifested by paresthesia and pain in the extremities, and eventually by loss of all sensation. Muscular weakness may accompany the sensory disturbances but usually there is little evidence of wasting or atrophy. The pathogenesis of the neuropathies is unknown, and there is no consistent relationship between the course of the neuropathy and that of the carcinoma. Neurologic symptoms may antedate the appearance of the tumor, and removal of the tumor often does not affect the neurologic symptoms.

Cortical Cerebellar Degeneration

Ataxia, dysarthria, nystagmus, intention tremor, and vertigo are manifestations of cortical cerebellar degeneration, not of metastasis. Such degeneration may be associated with the other neuromyopathies, of course; and it may occur as a separate entity. Pathologically there is degeneration of cells of the dentate nucleus with loss of fibers in the superior cerebellar peduncles and associated degeneration of various other spinal tracts.⁴ It is a problem to determine whether a metastatic lesion is present, and the importance of this decision to a surgeon planning thoracotomy is obvious.

Mental Changes

Dementia and toxic psychoses may occur, being associated usually with small-cell bronchogenic carcinoma. There may be marked mental deterioration or acute onset of hallucinations, agitation, confusion, and manic and uncooperative behavior. The patient may be totally resistant to management by the family or physician. The etiology is unknown; the syndrome could be due to electrolytic imbalance, but this is by no means certain. Treatment of the carcinoma improves the patient's behavior.

CARDIOVASCULAR MANIFESTATIONS

Thrombophlebitis

Many instances of thrombophlebitis occur as complications of obvious and far-advanced cancer. Lieberman and co-workers, however, in a review of 1400 cases of phlebitis, found that about one third of all those occurring in the presence of malignancy appeared before the tumor became obvious. Most commonly the tumor associated with phlebitis in males was broncho-

genic carcinoma; in females the reproductive organs were the most common primary site.

It has been shown recently by workers at this clinic that generation of thromboplastin is accelerated in patients with bronchogenic carcinoma.¹ The hypercoagulable state results from an increase of an antihemophilic globulin-like factor present in the plasma.

One should be very suspicious of malignancy, therefore, if a patient develops recurrent or migratory phlebitis without apparent cause—and especially if the phlebitis is resistant to anticoagulant treatment.

Non-bacterial Thrombotic Endocarditis

Although non-bacterial thrombotic endocarditis sometimes is called marantic endocarditis, yet it frequently occurs in the presence of an occult malignant lesion before any wasting or other manifestations of the tumor are present. Fibrinous vegetation without inflammation occurs on the cardiac valves; and this is capable of producing arterial embolization to the brain, coronary arteries, and other locations, causing sudden death.

Neufeld and others reported a case from the Mayo Clinic in 1960. The patient was a 45-year-old man who was in good health until one month before he died from multiple cerebral emboli. Before death he was thought to have a ruptured cerebral aneurysm. The thoracic roentgenogram indicated no abnormality, but at necropsy a mucus-producing adenocarcinoma was found in the apex of the left lung. The patient showed no evidence of wasting disease.

Nothing is known of the etiology, but the majority of the tumors in reported cases have been mucus-producing adenocarcinomas.

HEMATOLOGIC MANIFESTATIONS

Simple Chronic Anemia

Anemia associated with malignant disease is exceedingly common and is not necessarily indicative of metastasis or loss of blood. Most often it is normochromic, normocytic, and moderate in degree.¹⁰

Various mechanisms may be responsible. There may be decreased absorption of iron and consequent hypoferremia, or there may be hyperferremia with decreased utilization of iron and impaired erythropoiesis. Another cause of anemia may be increased hemolysis due to shortened survival of the erythrocytes.

Instances of disappearance of the anemia after removal of the tumor are common. Return of a depressed concentration of serum iron to normal after removal of a bronchogenic carcinoma has been reported.

Serum-Protein Abnormalities

Carpenter and associates found that neoplastic disease of the lung

was almost always associated with a marked derangement of the serum protein profile (SPP). Abnormalities of glycoprotein were observed in the early stages, before significant abnormalities of the protein pattern occurred. Most patients in the later phases of the disease also had elevated concentrations of alpha-1 protein and alpha-2 protein, and these abnormalities (plus the glycoprotein) were attributed to the inflammatory response around the tumor. In addition, however, bronchogenic carcinoma was associated frequently with elevation of beta-2 and gamma-1 glycoprotein. These have been shown by ultracentrifugation and immunoelectrophoresis to be 19 to 22 S macroglobulins not demonstrable in normal sera. They are not specific for bronchogenic carcinoma but frequently appear also in sera from patients with rheumatoid disease or hepatic cirrhosis.

Polycythemia

Carcinomatous polycythemia is distinguished from polycythemia vera and from secondary polycythemia by the absence of splenomegaly, the normality of oxygen saturation, and increase of the erythrocyte mass and plasma volume.⁹ An erythropoietin or erythropoietic stimulating factor is thought to be the cause when found with carcinoma of the lung, but this idea remains to be elucidated.

Purpura

Only rarely has bronchogenic carcinoma been associated with a bleeding diathesis due to deficiency of fibrinogen. A circulating fibrinolysin is the usual cause.²³

METABOLIC MANIFESTATIONS

Cushing's Syndrome

Since 1952, numerous cases of Cushing's syndrome associated with bronchogenic carcinoma have been reported.²⁵ Almost all of the lesions have been of the small-cell type. Some have metastasized to the adrenals, but some have not; and it is thought that metastasis has nothing to do with production of the syndrome.

In the past few years there have been several excellent reports of chemical and biologic studies attempting to determine the relation between bronchogenic carcinoma and Cushing's disease.^{16, 19, 20, 26} Perhaps the most extensive report is that of nine cases by Liddle and his associates. They analyzed the primary tumors, and in all found a polypeptide which was chemically and biologically the same as pituitary adrenocorticotrophic hormone. This substance was in circulating plasma also, in quantities sufficient to cause hyperplasia of the adrenal cortices and hypersecretion of corticosteroids. Analysis of the pituitary gland showed that the ability of this

gland to produce adrenocorticotropin had been suppressed. ACTH produced no increase of steroid excretion (urinary 17-hydrocorticosteroids), indicating that the adrenals were being maximally stimulated already. Furthermore, large doses of dexamethasone produced no significant suppression of corticosteroid excretion, indicating that the production of adrenocorticotropin by the tumor was not governed by the normal regulatory mechanism. That is, the tumor itself seemed autonomous in its excretion of this substance and in the production of Cushing's syndrome.

Vogel and his co-workers reported from this clinic one case with metastasis to adrenals. The patient was a 40-year-old housewife who six months prior to admission had had pneumonia, which was followed by persistent weakness, fatigue, and cough. Four weeks prior to admission her parents had noted an abrupt change in appearance with facial swelling, growth of hair around the face, and a staring expression. She then had become hyperactive and developed manic behavior, working 22 hours a day cleaning house. This was followed by exhaustion and somnolence.

On examination she was florid and showed the typical appearance of Cushing's syndrome, with facial hirsutism. Confusion was evident. On roentgenograms the head and chest appeared normal. Blood cortisols measured 78.7 micrograms/100 ml. at 8 A.M. and 77.4 at 4 P.M. Three days after admission pneumonitis developed in the right upper lobe, and three days later the patient became comatose and died. Necropsy revealed a bronchogenic carcinoma of small-cell type in the right upper lobe with metastasis to hilar lymph nodes, pericardium, liver, abdominal lymph nodes, ribs, vertebrae, and right ovary. The adrenals also contained metastatic lesions and the cortices were thickened, measuring 3 to 5 mm.

Nichols and Gourley reported two cases of bronchogenic carcinoma without Cushing's syndrome but with bilateral adrenal cortical hypertrophy. The tumors were devoid of corticotropin with corticosteroid-releasing capacity, but had an extractable corticotropin-like material with capacity to maintain adrenal weight in hypophysectomized rats. This suggests that there may be different types of corticotropin and may explain the bilateral cortical hypertrophy occasionally found in patients with bronchogenic carcinoma but without Cushing's syndrome.

Renal Loss of Sodium

The syndrome of hyponatremia with excessive renal loss of sodium in association with bronchogenic carcinoma has been described. It probably results from the inappropriate secretion of antidiuretic hormone. Some of the cases have exemplified a dilutional type of hyponatremia.²⁹ All of the pulmonary carcinomas have been of the small-cell variety.

A patient (reported by Dr. H. K. Ivy) came to the Mayo Clinic because of weakness and episodes of dizziness for approximately nine months, but especially during the month preceding admission. He had almost lost consciousness on several occasions. Postural hypotension was demonstrated

and Addison's disease was suspected. The serum concentration of sodium was found to be 108 mEq./L., and 105 when rechecked. Extensive studies of electrolyte balance demonstrated a "salt-losing nephritis," presumably due to an old chronic pyelonephritis. The chest roentgenogram showed only slight "reticular fibrosis."

The patient's family wished to take him home after approximately two weeks of hospitalization, but he soon was re-admitted with an acute toxic psychosis marked by hallucinations, confusion, and belligerent behavior. This subsided rapidly following administration of intravenous saline.

Urinary retention developed without evidence of urethral obstruction, and sweat tests demonstrated a total inability to sweat except on the palms of the hands. These abnormalities together with the postural hypotension suggested an autonomic neuropathy. Continued sodium loading brought the serum sodium to 125 mEq./L., and the patient seemed improved. He was dismissed with a prescription of 12 gm. of sodium chloride daily as a dietary supplement.

Two months later he returned for further study at his physician's request. The clinical improvement had been maintained. A recheck thoracic roentgenogram, however, showed a mass in the right hilum; and bronchoscopic examination demonstrated a small-cell type of bronchogenic carcinoma. Nitrogen mustard and roentgen therapy were administered, and thereafter no difficulty was encountered in maintaining the serum sodium at normal levels even though a low-salt regimen was imposed. But postural hypotension, urinary retention, and lack of sweating continued. The patient died three months later, or five months after his first visit to this clinic.

This case, of course, raises the problem of multiple syndromes: renal loss of sodium, autonomic neuropathy, and a toxic psychosis. It is interesting that the psychosis disappeared when salt was administered.

Hypercalcemia

When reports of hypercalcemia associated with malignancy began to appear, it was assumed that the elevation of serum concentrations of calcium was due to mobilization of this element from the bones because of metastasis. In the past six or seven years, however, it has been realized that hypercalcemia can occur in malignant disease without any spread to bone. All investigations have failed to disclose any anatomic or physiologic explanation.

Symptoms and clinical signs include deterioration of intellect, confusion, somnolence, and episodes of coma. Diffuse alterations may be seen in the electroencephalogram. In relation to gastrointestinal activity, there is loss of appetite, nausea, vomiting, and constipation; and sometimes there is thirst, polydipsia, polyuria, albuminuria, and renal failure. In the cardiovascular system there may be tachycardia, arrhythmia, electrocardiographic abnormalities, and increasing predilection toward toxic manifestations of digitalis. Neurologically there may be marked muscular weakness,

hypotonia, and hyporeflexia. All of these findings are most common with breast carcinoma, but a significant number have accompanied carcinoma of the lung without demonstrable metastasis.

Locks studied 119 patients with bronchogenic carcinoma and found hypercalcemia in 13 per cent. Less than 2 per cent, however, afforded symptoms or signs of hypercalcemia. Skeletal metastasis was found in 9 per cent of patients with normal serum concentrations of calcium, but 50 per cent of those with excess serum calcium had metastasis. Resection of the tumor in cases without metastasis was followed by decrease of serum calcium, and chemotherapy also resulted in temporary improvement. Steroid therapy lowered the serum calcium in one patient but did not in another. Locks stated that the level of serum calcium may serve as a useful index in ascertaining effect of therapy for the malignant process. With steroid therapy the serum calcium frequently falls if hypercalcemia is due to bronchogenic carcinoma, whereas it does not fall when due to hyperparathyroidism. However, it usually takes two weeks or more of treatment before the level declines sufficiently to be diagnostic.

Gynecomastia

Gynecomastia is a semiphysiologic phenomenon at puberty, may occur in normal men who seem normal generally, and may be a manifestation of aging. Williams, in routine gross and microscopic examinations of 447 consecutive males, found gynecomastia discernible grossly in four but indicated histologically in 40 per cent. She divided the cases into florid and quiescent fibrotic types. Some with bronchogenic carcinoma—usually adenocarcinoma—fell into each group.

In two patients not of that series,^{8, 12} circulating concentrations of estrogen were found to be elevated abnormally; and gynecomastia regressed when the tumor was removed from one of these patients.⁸

COMMENT

The oft-times nebulous-appearing association of the various extrathoracic manifestations of bronchogenic carcinoma has been seen with sufficient frequency to preclude the skeptics' impression of simple coincidence. It is true that we lack adequate explanations for these bizarre associated signs and symptoms (and that some may appear with other primary malignant lesions elsewhere in the body), but this need not detract from the importance of recognizing them and their potentiality for aiding in the earlier diagnosis and treatment of these discouraging lung cancers. As much as we would hope these extrathoracic manifestations would be early signs, and therefore helpful, we must accept their ominous import in many instances. Because they may be the source of extreme discomfort, even palliative treatment directed toward hopeless broncho-

genic lesions is encouraged for the possibility that the effects of the associated syndromes will be relieved.

Over and above presenting the association of these unusual signs and symptoms with respect to recognition of the lung lesion, we would be negligent if we did not mention the challenge their presence poses for the thoracic surgeon who is constantly alert to avoid thoracotomy in patients who have metastases elsewhere in their body. It would not be difficult to accept many of the above-mentioned symptoms and signs as manifestations of metastasis. It is an obvious responsibility of physicians and surgeons to be knowledgeable about these unusual associations of bronchogenic carcinoma and their amenability to curative or palliative treatment. In addition, the surgeon will be especially grateful for the correct preoperative preparation of those unfortunate patients with metabolic derangements that add substantially to risks of surgery unless controlled.

Familiarity with the extrathoracic manifestations of bronchogenic carcinoma not due to metastatic lesions can lead to longer, if not more comfortable, survival for these patients. Diligent investigation of these unusual signs and symptoms, sometimes associated with other primary malignant tumors, may contribute substantially to our knowledge of the frustrating and discouraging lung cancers as well as malignant lesions in general.

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Thoracic-Inlet Tumors

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In 1838, Hare described what is probably the first reported case of tumor involving the pulmonary apex, the brachial plexus, and the sympathetic chain. In 1932, Tobias described in detail the clinical syndrome produced by malignant developments in this region and called it the apico-costo-vertebral syndrome.

However, Pancoast drew most attention to this clinical problem by papers published in 1924 and 1932. From his experience with seven cases he described a group of findings which have since been called the Pancoast syndrome: (1) pain about the shoulder and down the arm; (2) atrophy of the hand muscles; (3) Horner's syndrome; and (4) roentgenographic evidence of a small lesion at the extreme apex of the lung, usually with local destruction of ribs or vertebrae. Because this tumor had features considered atypical for primary carcinoma of the lung, he suggested that it arose from an extrapulmonary structure—perhaps from some embryologic rest such as the fifth branchial pouch. To indicate the uncertain origin, he named it “superior pulmonary-sulcus tumor.”

Since 1932 it has been generally accepted that a malignant growth producing this clinical pattern is usually a carcinoma of the lung arising in the very apex and involving the extrapulmonic structures in this region by direct extension. Although Pancoast stated that the tumor is likely to be of the squamous-cell variety, it may be glandular or epithelial in origin and produce a complete or incomplete Pancoast syndrome. Benign tumors, inflammatory and infectious processes arising in the apex of the lung or adjacent structures, and tumors of bone and sympathetic nerves also have been known to produce the same clinical effect.

However, there is reason to wonder whether on occasion the malignant neoplasm producing this syndrome may not arise from some extrapulmonary structure in the apex of the thorax^{2, 5, 9, 13} or in a subpleural apical scar⁷ with extension into the lung and adjacent structures. Because of the uncertain origin of the tumor in all instances, a variety of names have been proposed. Correctly speaking, the term *superior pulmonary-sulcus tumor*

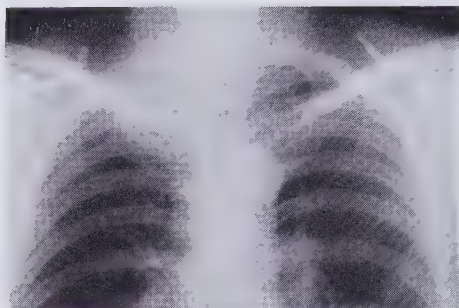


Figure 1. Obvious tumor involving apex of right lung.

employed by Pancoast should be reserved for a neoplasm believed to arise from an extrapulmonary structure. If the tumor arises in the apex of the lung, it is simply carcinoma of the lung producing the Pancoast syndrome. Inasmuch as it is impossible to establish the origin of all tumors occurring in this area, an inclusive term such as thoracic-inlet tumor⁵ seems appropriate.

CLINICAL PATTERN

Whatever the origin of the tumor, the clinical pattern is quite constant. It occurs more commonly from the fourth decade on. Herskovic and associates found that 71 of 76 patients were males. When these 76 cases are added to the 151 reviewed by Herbut and Watson, the ratio of males to females is 12:1. The right side is involved in 56 to 60 per cent of cases.^{5, 6}

Pain is the initial, most frequent, and outstanding symptom—as might be anticipated from the fact that the brachial plexus and bony structures nearby are usually involved. Ordinarily the pain is described as a constant, progressively increasing ache located in the interscapular, shoulder, or upper anterior chest region and ultimately spreading to the medial aspect of the upper extremity. Because of the nature of the pain, the orthopedist or neurosurgeon frequently is consulted early in the course of the disease and such diagnoses as periarthritides of the shoulder or possible spinal-cord tumor are entertained.

Involvement of the nervous system, with resultant signs and symptoms therefrom, occurs commonly because of the proximity of certain nerve structures. Extension of the tumor across the pleura involves the inferior trunk of the brachial plexus, which is made up of the eighth cervical and first thoracic spinal nerves with a contribution from the second thoracic segment. Involvement of these nerves accounts for the pain felt in the medial aspect of the upper extremity, weakness and atrophy of the small muscles of the hand, and (noted sooner and more frequently than atrophy of muscles) absence of the triceps reflex. Involvement of the inferior cervical or cervicothoracic ganglion (near the neck of the first rib)

produces the commonly seen Horner's syndrome consisting of miosis, enophthalmos, and anhidrosis on the same side of the face and upper extremity. Less often the tumor compresses the spinal cord at the level of the first and second thoracic vertebrae, producing the expected symptoms of a spinal-cord tumor at this level and leading, on occasion, to surgical exploration for a primary spinal-cord tumor. Also, the recurrent laryngeal nerve may be involved with resulting hoarseness.

Pulmonary symptoms are relatively infrequent and rarely the presenting complaint, although cough and hemoptysis have been noted. The physical signs of dullness and absence of breath sounds over the pulmonary apex may be found occasionally. There may be a supraclavicular mass, or spread of the tumor may involve a supraclavicular lymph node. Pleural effusion was not seen in any of 76 cases.

Of major importance in the evaluation of a patient with such symptoms is careful roentgenographic study of this region. In most instances the roentgenogram of the thorax will disclose an obvious tumor involving the apex of the lung (Fig. 1). If not apparent on the roentgenogram of the thorax, films for osseous details may show involvement of the proximal ends of the first two ribs and somewhat less frequently destruction of the lateral aspect of the bodies of the first two thoracic vertebrae and less frequently the third rib and thoracic vertebra. Under these circumstances the diagnosis is not difficult. Sometimes, however, the tumor grows in a plaque-like fashion over the apex of the lung, producing on roentgenograms only the changes typical of some apical pleural thickening (Fig. 2), a lesion commonly reported among generally normal findings. A report of apical pleural thickening in a patient with shoulder or arm pain on the same side must be viewed with a great deal of suspicion, and further efforts must be made to determine the nature of the shadow. Findings from special studies of the ribs and vertebrae frequently are normal in such cases because the

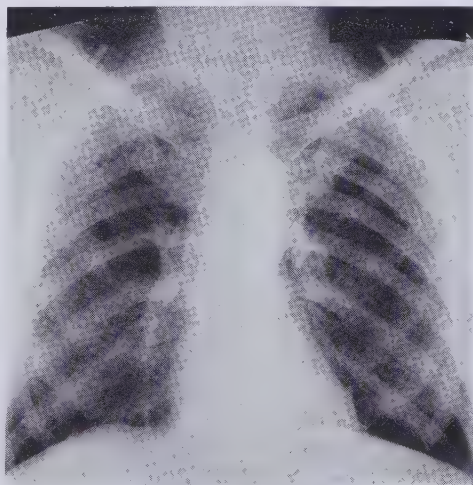


Figure 2. Thoracic-inlet tumor presenting as minimal pleural thickening at apex of left lung.

tumor has not yet involved bone enough to be visible roentgenographically. Other diagnostic procedures to be mentioned later are then in order.

DIAGNOSIS

Although the great majority of lesions involving the apex of the lung and producing Pancoast's syndrome are malignant, on occasion the pattern has been produced by a nonmalignant lesion. Therefore it is important to establish the diagnosis of malignancy as securely as possible.

The routine laboratory tests are of little help in this regard. The lesion is beyond the range of visualization through the bronchoscope. On occasion examination of the sputum will demonstrate carcinoma cells. Perhaps the usefulness of this examination can be increased if the technique for inducing sputum is used more often. Biopsy of supraclavicular masses and enlarged cervical nodes, when present, will yield the diagnosis most readily; and it behooves the physician to examine the supraclavicular region and neck carefully when evaluating a patient with an intrathoracic tumor.

There will remain a number of cases with clinical evidence of a lesion involving the brachial plexus and the apex of the lung in which a diagnosis cannot be made without surgical exploration. Thoracotomy or such an approach as would be used for a cervical sympathectomy as recently proposed by McGoon is then indicated. At times when the clinical pattern is that of malignancy and histologic confirmation of the diagnosis is not feasible, treatment will have to be carried out on the strength of only a clinical diagnosis.

TREATMENT AND PROGNOSIS

In his second paper Pancoast commented on the very poor prognosis to be expected, and his predictions have been borne out. Death usually occurs within a year of the time the diagnosis is made.

Since complete surgical extirpation of this lesion is not feasible, most patients have been treated with irradiation. At the present, heavy irradiation is our choice of therapy for apparently well-localized lesions. Pain frequently is lessened.

Attempts have been made to improve therapeutic results by combining irradiation and surgical resection of the tumor.^{3, 12} It is noteworthy that several authors^{1, 3, 11, 12} have found that surgical excision of even a portion of the tumors seemed to reduce pain significantly.

Herskovic, upon reviewing the experience at this institution, found that two patients in 76 have survived more than five years following irradiation therapy alone and one patient has survived more than five years after incomplete surgical excision followed by irradiation. The loca-

tion of these tumors allows high-dose roentgen therapy, a factor which may account for the favorable response to this treatment in some cases. Undoubtedly irradiation will be more successful if the diagnosis can be made and treatment instituted early in the course of the process.

The severe and constant pain which most of these patients suffer cannot be adequately controlled at all times with analgesics alone. Consideration should then be given to spinothalamic tractotomy.

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Surgical Treatment of Solitary Metastatic Pulmonary Lesion

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The appearance of an abnormal shadow in the thoracic roentgenogram of a patient who previously has had a malignant neoplasm in some other portion of the body is an ominous development. It usually indicates that spread of the tumor to the lungs has occurred and that a progressive downhill course can be anticipated, despite any therapy that can be provided. In most instances of pulmonary metastasis the lesions are multiple and bilateral. However, in recent years it has become apparent that in some instances—months or years after apparently successful surgical resection of the primary neoplasm—a solitary metastatic pulmonary lesion may appear.

In carefully selected cases of solitary pulmonary metastasis, surgical resection of the lesion has provided very gratifying results. During the years 1941 through 1959, a total of 169 resections for such tumors in the lung were performed on 165 patients at the Mayo Clinic. The overall five-year survival rate in these patients was 31 per cent. While this is not so good as would be desired, it actually compares very favorably with the results of surgical resection of primary pulmonary carcinomas. Since there is no other effective treatment to offer these patients and the prognosis is hopeless without surgical resection, we believe that carefully selected patients with solitary pulmonary metastatic lesions should be offered operation.

Incidence and Primary Source of Metastatic Pulmonary Tumors

Although metastatic pulmonary lesions are much more often multiple than solitary, it is important to realize that solitary lesions can occur. Accurate estimation of the incidence of solitary metastatic lesions as compared to multiple lesions is not yet possible, but it is becoming apparent that primary neoplasms in certain sites are more likely to be complicated by solitary pulmonary metastasis than those in other sites (Table 1). For

Table 1. *Site of Primary Tumor Among 165 Cases of Solitary Metastatic Pulmonary Lesion*

SITE OF PRIMARY TUMOR	NUMBER	PER CENT
Rectosigmoid.....	36	21.8
Breast.....	21	12.7
Colon.....	16	9.7
Kidney.....	12	7.3
Skin.....	12	7.3
Melanoma.....	9	5.5
Squamous-cell epithelioma.....	3	1.8
Cervix.....	11	6.7
Testes.....	7	4.2
Cylindroma (various sites).....	6	3.6
Uterus.....	3	1.8
Ovary.....	3	1.8
Thyroid.....	2	1.2
Bladder.....	2	1.2
Jejunum.....	1	0.6
Jaw.....	1	0.6
Vagina.....	1	0.6
TOTAL.....	134	81.1

example, 30 per cent of the metastatic lesions in our series mentioned had arisen from primary tumors in the rectum and left colon. Other relatively common primary sources of solitary pulmonary metastatic lesions were malignant lesions of the breast, kidney, uterus, and ovaries, and sarcomas of the extremities. It has become apparent that any patient who has had a malignant tumor in any of these sites should be given careful periodic examinations with thoracic roentgenography, so that pulmonary metastasis can be detected as early as possible. Table 2 shows the incidence of different types of sarcoma among the primary lesions.

Table 2. *Kinds of Sarcoma as Primary Lesions Among 165 Cases of Solitary Metastatic Pulmonary Lesion*

TYPE OF SARCOMA	NUMBER
Fibrosarcoma.....	8
Chondrosarcoma.....	4
Osteogenic sarcoma.....	5
Synovial-cell sarcoma.....	2
Liposarcoma.....	2
Ewing's tumor.....	2
Undifferentiated sarcoma.....	1
Alveolar-cell sarcoma.....	1
Leiomyosarcoma.....	2
Rhabdomyosarcoma.....	1
Mesenchymoma.....	1
Hemangiopericytoma.....	2
TOTAL.....	31 (19%)

Diagnosis

The diagnosis of pulmonary metastatic lesions depends largely on thoracic roentgenograms. The patients have relatively few symptoms, because such lesions usually develop in the parenchyma of the lung near its periphery. In most instances the bronchi are not extensively involved, and cough is usually not a prominent symptom. Cytologic examination of the sputum for malignant cells has been helpful in a relatively small percentage of cases. Recent experience with aerosol induction of sputum has shown that cancer cells can be demonstrated in the sputum in approximately 50 per cent of cases of metastatic carcinoma. The usual peripheral location of the lesions severely restricts the usefulness of bronchoscopic examination. Thoracic roentgenograms—and when indicated, tomograms—are by far our most valuable means of diagnosis. Ordinarily these lesions appear as rounded, uncalcified, “coin-type” shadows.

Indications for Operation

Obviously thoracotomy and resection of what appears to be a solitary metastatic pulmonary lesion is not a procedure to be taken lightly and should not be performed unless definite criteria have been satisfied. 1. All available information regarding the primary lesion and its surgical treatment should be obtained and reviewed. It should indicate that the primary lesion was removed completely, that the surgeon who had performed the operation was satisfied that it had been adequate, and that in his opinion a favorable prognosis could be anticipated. 2. Thorough examination of the patient should not show any evidence of any recurrent or metastatic disease other than the pulmonary lesion. 3. Careful review of the thoracic roentgenograms should afford no evidence of metastatic disease in the opposite lung. 4. The patient's age and general condition should be such as to justify the operation planned. 5. The patient and his family should understand clearly the nature of the problem and its seriousness. 6. In most instances it is advisable to send the patient home for a three-month period of observation after the pulmonary lesion is discovered, and then to examine him thoroughly again before proceeding to operate. This three-month delay does not appear to be detrimental to the patient who has a lesion suitable for operation, and it provides an opportunity for other metastatic lesions not apparent on the earlier examination to develop to a point where they can be detected in some instances. The observation period has enabled us to avoid performing what would have been a futile operation in some cases.

Surgical Treatment and Results

We are convinced that a pulmonary resection performed for metastatic disease should be as conservative of lung function as possible. In most

instances lobectomy or even segmental resection provides as effective treatment as a more extensive operation. Hilar lymph nodes are not often involved, and the usual peripheral location of the lesions makes a limited pulmonary resection technically possible in most instances. In only 20 per cent of our cases did the location of the lesion require pneumonectomy. The hospital mortality in the series as a whole was 1.2 per cent. Follow-up studies revealed that 71 per cent of the patients survived one year, 48.7 per cent two years, 35.4 per cent three years, and 31 per cent five years. Patients requiring pneumonectomy had a 28 per cent five-year survival rate, and the rate for those requiring a less extensive pulmonary resection was 50 per cent. This fact supports our view that conservative pulmonary resection is to be preferred when technically possible.

COMMENT

It is important to recognize that with appropriate surgical resection, the prognosis accompanying solitary metastatic pulmonary lesions is not hopeless. There is no other effective treatment to offer. Our experience indicates that in carefully selected cases the outlook is really hopeful and certainly equal to that accompanying many well-established operations for primary carcinoma and sarcoma. The operations have carried remarkably little hospital mortality and disability.

It is of considerable interest that experience has been most favorable with solitary pulmonary lesions that had originated from primary tumors in the lower part of the abdomen or the lower extremities. We have had some favorable results where the primary tumor sources involved the breast, head and neck, and upper extremities; but it is apparent that the lower left colon and rectum, the uterus and ovaries, the kidneys, and the testes are the most favorable sites of the primary neoplasm.

Some evidence suggests that the longer the period that elapses between surgical resection of the primary tumor and the development of pulmonary metastatic growths, the better the prognosis. But this evidence, though suggestive, is not conclusive.

The criteria for selection of cases of pulmonary metastasis in which pulmonary resection is justified have broadened gradually with experience. Multiple lesions, provided they are all in one lung, do not necessarily indicate inoperability, although the survival rate of patients with multiple lesions is considerably poorer than that of patients with a single lesion.

It should be pointed out that a solitary lesion developing in the lung of a patient previously treated for a malignant growth elsewhere in the body is not necessarily a metastatic carcinoma. The new lesion may be a new primary neoplasm or even a benign lesion. This can be determined only by thoracotomy and excision of the tumor, but the fact that the

pulmonary lesion may not be related to the previous neoplasm adds to the importance of treating these lesions surgically.

SUMMARY AND CONCLUSIONS

Metastatic pulmonary lesions that are solitary or localized enough to warrant consideration of surgical excision occur not infrequently. Thoracic roentgenograms should be obtained as a part of the routine annual examination of all patients who have had a malignant tumor treated surgically, so that pulmonary metastasis can be detected as early as possible. In carefully selected cases, surgical treatment of pulmonary metastatic lesions provides gratifying results with little risk or disability.

Bronchial Tumors Originating from Mucous Glands

Current Classification and Unusual Manifestations

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The current classification of primary malignant tumors of the lung²¹ includes several subtypes apparently of mucous-gland origin which often are grouped together under the heading "bronchial adenoma" (Table 1). Although entrenched by historical usage, the term "adenoma"—implying a benign glandular neoplasm—is unsatisfactory as a name for the group. Carcinoid tumor is the most common type; and although usually localized, it occasionally does metastasize. Cyndroma, albeit slow-growing, is a particularly lethal type of adenocarcinoma. The mucoepidermoid tumor and mixed tumor are rare and considerably less aggressive bronchial lesions, but are at least locally malignant.

Table 1. *Classification of Primary Malignant Tumors of the Lung*

Bronchial epithelial origin

- Bronchogenic carcinoma
 - Squamous-cell carcinoma
 - Adenocarcinoma
 - Large-cell carcinoma
 - Small-cell carcinoma
 - Alveolar-cell carcinoma (terminal bronchiolar)

Mucous-gland origin

- Carcinoid tumor
- Cyndroma (adenoid cystic carcinoma)
- Muco-epidermoid tumor
- Mixed tumor

Mesenchymal origin

- Lymphosarcoma
 - Fibrosarcoma
-

CLINICAL AND PATHOLOGIC FEATURES

These various subtypes, while differing in the frequency of metastasis and degree of malignancy, do share certain features, including slow growth, frequent polypoid structure, and a commonly accepted origin from the bronchial mucous glands. For these reasons it appears logical and convenient to consider the subtypes as a somewhat related group.

Bronchial tumors of mucous-gland origin are much less frequent than bronchogenic carcinoma. In a recent review of Mayo Clinic material¹² these tumors constituted approximately 6 per cent of all primary malignant lesions of the lung. Unlike bronchogenic carcinoma, they occur with equal frequency among men and women, reaching a peak incidence at the relatively young age of 45 years. Although the symptoms of bronchial irritation and obstruction are shared with other tumors of the lung, symptoms accompanying this group tend to be of longer duration, often extending over several years.

The carcinoid tumor is identical histologically with its counterpart in the gastrointestinal tract and likewise produces on occasion the so-called "carcinoid syndrome" through its elaboration of serotonin. The other subtypes are identical in structure with their counterparts in major or minor salivary glands. Such tumors have not been associated with hormonal function.

Grossly, the carcinoid tumor has been compared to the well-known iceberg, for varying amounts of the tumor present as an endobronchial mass but ordinarily the greater part is extrabronchial. Although this iceberg configuration is the usual finding, entirely extrabronchial and entirely endobronchial carcinoid tumors are encountered. Because the latter group make up only about 10 per cent of the total, eradication by endoscopic means is seldom attempted.

The approximate location of carcinoid tumors in 124 patients who underwent surgical treatment at the Mayo Clinic is illustrated in Figure 1.

124 CARCINOID TUMORS

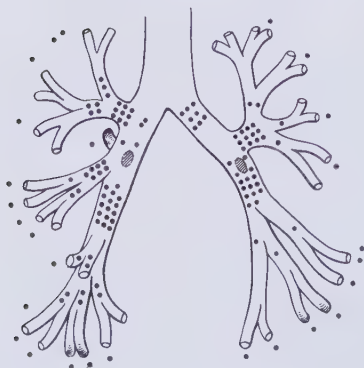


Figure 1. Location of 124 carcinoid pulmonary tumors.

Approximately 60 per cent of these tumors could be visualized at the time of bronchoscopy. It should be noted that the tumors, unless ulcerated, are covered with bronchial epithelium and thus do not shed tumor cells in the sputum or bronchial secretions. Regional or distant metastasis is noted in 10 per cent of cases.

The location of seven surgically resected cylindromas of the bronchus and the approximate location and gross form of four muco-epidermoid tumors of the bronchus are illustrated in Figure 2, *a* and *b*. The cylindroma (or adenoid cystic carcinoma) of the bronchus is a slow-growing, markedly infiltrative carcinoma whose gross features may be sometimes polypoid or sometimes quite comparable to those seen in bronchogenic carcinoma. It has a marked tendency to involve the major bronchus and carina. With this type of neoplasm, bronchial secretions or sputum may be positive for malignant cells. Muco-epidermoid tumors tend to present as pedunculated polypoid endobronchial growths, although one example (Number 1 in Fig. 2, *b*) was entirely extrabronchial. These tumors in the bronchus were locally infiltrative, but no evidence of distant metastasis from them has appeared.

Mixed tumors of salivary-gland type, although rare, can occur in the bronchial tree as illustrated by the following case report.

CASE 1. A 50-year-old woman was first seen in September, 1953, for evaluation of "atelectasis" of the right lower lobe. In the preceding May she had had an attack of pneumonia, for which antibiotics had been given. Recovery was not rapid, and a productive cough continued ($\frac{1}{4}$ cup sputum daily) with occasionally a pink tinge to sputum but no frank hemoptysis. One week prior to admission here, a

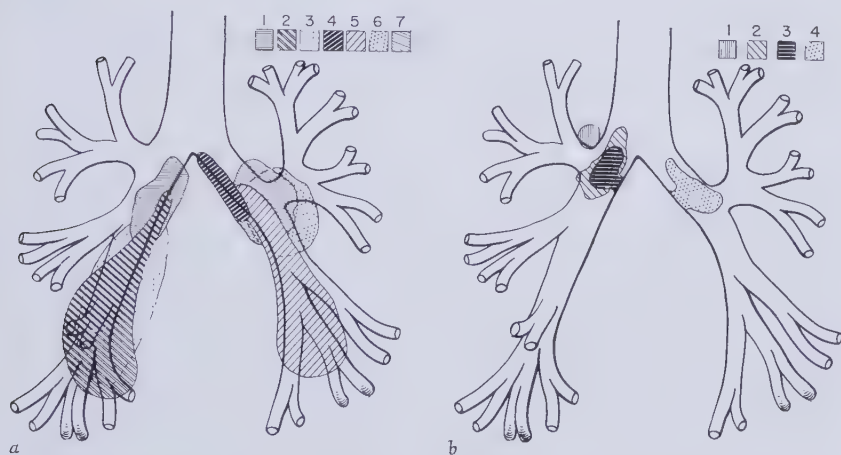


Figure 2. Location and extent of tumors of bronchus. *a*, Seven cylindromas (adenoid cystic carcinomas). *b*, Four muco-epidermoid carcinomas. (From Payne, W. S., Ellis, F. H., Jr., Woolner, L. B., and Moersch, H. J.: The surgical treatment of cylindroma [adenoid cystic carcinoma] and mucoepidermoid tumors of the bronchus. *J. Thoracic Surg.* 38: 709-726 [Dec.] 1959. By permission of the C. V. Mosby Company.)

roentgenogram of the thorax had been made, after which she had been referred for evaluation.

On admission she was found to have dullness and depressed breath sounds at the right base posteriorly. The roentgenogram of the chest revealed complete collapse of the right lower lobe with a shift of the mediastinum to the right. A poorly defined right hilar mass was noted. Bronchoscopic examination revealed a large polypoid tumor in the bronchus of the right lower lobe, and it bled easily on manipulation. On September 30, thoracotomy was carried out and a large, firm tumor was found arising from the right bronchus intermedius just below the upper-lobe bronchus and extending deep into the hilus. The right middle and lower lobes were contracted and airless. The right middle and lower lobes were resected. The polypoid portion of the tumor measured 1 by 0.5 cm. and the extraluminal portion 2 cm. in diameter.

Second Admission. The patient returned in April, 1961. She had no chest symptoms except for chronic cough producing a moderate amount of sputum. Cytologic examination of the sputum disclosed no tumor cells. Roentgenography of the chest revealed evidence of the prior thoracotomy and a nodular lesion medially, projected over the anterior end of the right clavicle. Thoracotomy was done. A recurrent tumor mass was noted around the bronchial stump, and also three tumor implants up to 2 cm. in diameter in the hilar region and near the azygos vein and on the diaphragm. The right lung was resected. Histologic examination of original and recurrent tumor shows an intimate mixture of benign-appearing glandular epithelium with a myxoid connective-tissue stroma undergoing focal chondroid metaplasia. The pathologic diagnosis was mixed tumor of salivary-gland type, primary in bronchial mucous glands.

The behavior of the tumor in this case, including its slow rate of growth and the tendency to recur in multiple nodules after surgical resection, is entirely comparable to that observed in mixed tumors of the salivary-gland type elsewhere in the body. The mixed tumor in salivary glands is commonly classified as benign, though carcinomatous transformation (so-called malignant mixed tumor) does occur. In addition, local recurrence of mixed tumor and invasion of adjacent structures may sometimes cause death in the absence of distant metastasis.

TREATMENT OF TUMORS OF MUCOUS-GLAND ORIGIN

The treatment of mucous-gland tumors of the bronchus varies with the type involved. For the pedunculated carcinoid of the bronchus, one may consider endoscopic removal or local excision and plastic reconstruction of the bronchus. Ordinarily, however, considerable bronchial obstruction and pulmonary inflammation and bronchiectasis are associated with these obstructive lesions; and some form of pulmonary resection is required. Endoscopic resection therefore is usually reserved for the uncomplicated polypoid endobronchial carcinoid with a relatively long pedicle and for the severely debilitated patient. These same general rules apply to the mucoepidermoid and mixed-tumor types. Even so, in our experience all of the

mucoid-epidermoid tumors have required pneumonectomy because of their location and because of marked suppurative complications in the involved lung. For cylindroma of the bronchus, which requires aggressive surgical treatment, palliative pneumonectomy offers the best chance for long-term survival and is preferable to endoscopic palliation, which has been shown to be ineffective in relieving the severe suppurative complications associated with this tumor. Radiation therapy is not of proved value in the management of any of the subtypes.

UNUSUAL MANIFESTATIONS OF CARCINOID TUMORS

Since the carcinoid tumor is by far the most commonly encountered, the cases that follow were selected to illustrate various uncommon manifestations of this type of tumor.

Endobronchial Location

It has been estimated that approximately 10 per cent of bronchial carcinoids are truly endobronchial.^{18, 27} Pedunculated carcinoids are rarer still,¹⁷ although mucoid-epidermoid tumors commonly present in this fashion. When a carcinoid is entirely endobronchial, the thorax may appear normal on the standard roentgenogram, and the symptoms may simulate chronic bronchitis or asthma.

CASE 2. A 66-year-old woman came to the Mayo Clinic for a routine general examination. She was somewhat dyspneic on exertion and had a dry cough. The only significantly abnormal finding on physical examination was moderate elevation of the blood pressure. The lungs seemed normal on auscultation, and a thoracic roentgenogram showed nothing extraordinary.

She returned after six months, during which interval wheezing had developed. A diagnosis of asthmatic bronchitis had been made elsewhere and she had been treated for that disorder—with *improvement*. A peculiar inspiratory stridor was noted, and auscultation of the lungs disclosed inequality of the breath sounds on the two sides, those on the left being louder and more coarse. Again the thoracic roentgenogram was normal (Fig. 3, *a* and *b*). Bronchoscopic examination revealed a polypoid, pedunculated tumor almost completely occluding the left main bronchus. The tumor proved to be a bronchial adenoma of the carcinoid type, attached by a thin pedicle to the medial wall of the left main bronchus opposite the orifice of the left upper lobe. The tumor was removed endoscopically and its base was fulgurated. Two yearly follow-up examinations have disclosed no evidence of recurrence (Fig. 3, *c*).

This case serves to emphasize the fact that all that wheezes is not necessarily asthma. This is particularly true if the wheeze is unilateral or well localized. In such a situation inspiration-expiration roentgenograms of the thorax, fluoroscopic examination, tomography, and bronchoscopy may be quite helpful, as the next case demonstrates.

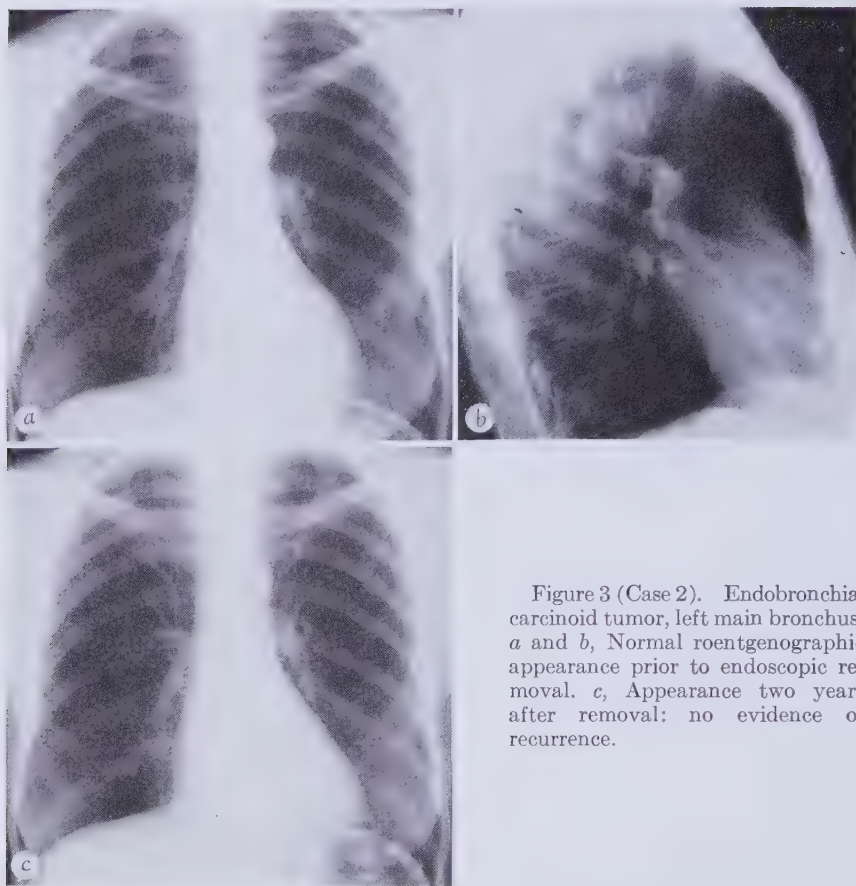
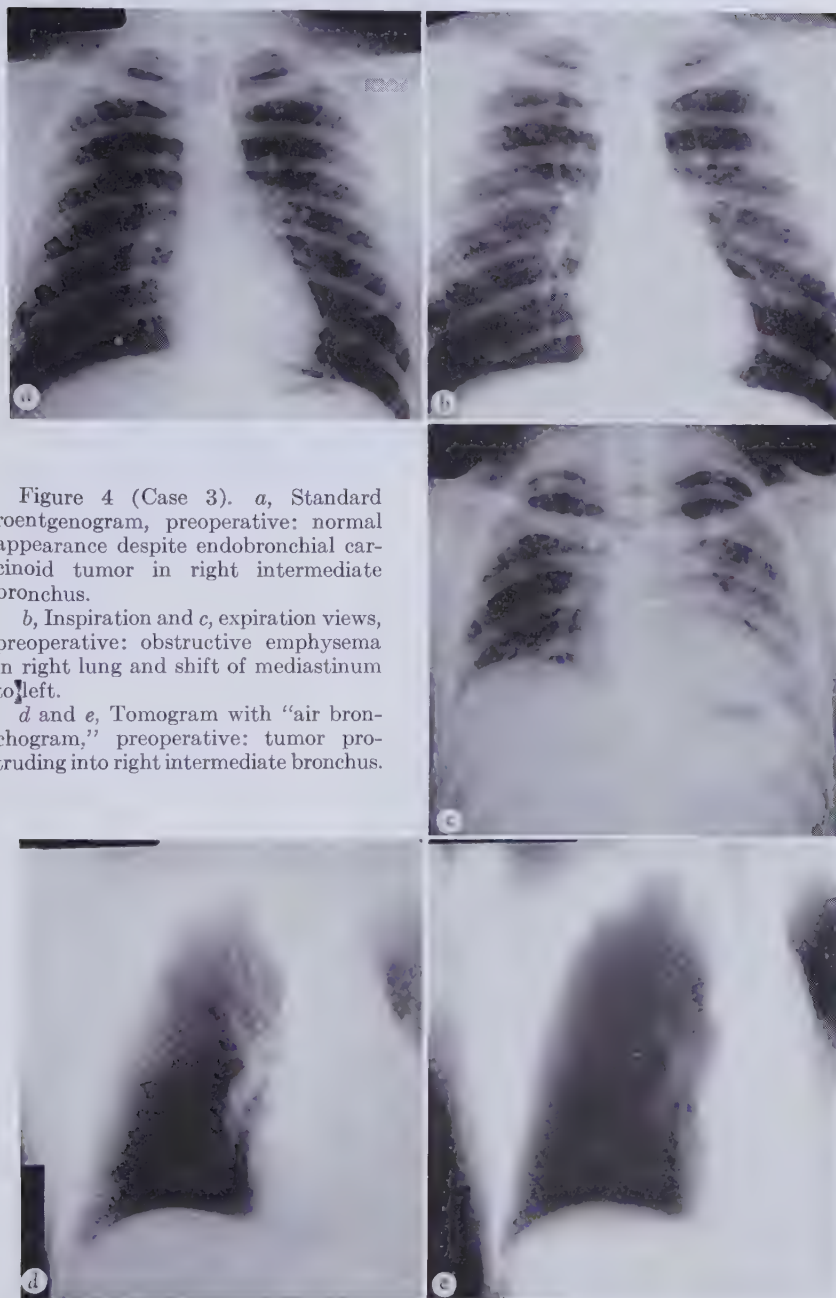


Figure 3 (Case 2). Endobronchial carcinoid tumor, left main bronchus. *a* and *b*, Normal roentgenographic appearance prior to endoscopic removal. *c*, Appearance two years after removal; no evidence of recurrence.

CASE 3. A 22-year-old man had consulted his home physician because of symptoms of exertional dyspnea and intermittent hemoptysis present for one year. Findings on examination had been normal, except for an inspiratory and expiratory wheeze heard over the right lung; and a standard thoracic roentgenogram had shown no abnormality (Fig. 4, *a*). Fluoroscopy and inspiration-expiration roentgenograms of the thorax had, however, indicated obstructive emphysema of the right lung and a shift of the mediastinum to the left on expiration (Fig. 4, *b* and *c*). Tomograms of the right hilus had revealed a rounded lesion protruding into the right intermediate bronchus (Fig. 4, *d* and *e*). Bronchoscopic examination had demonstrated a polypoid bronchial carcinoid (Fig. 5), which had been resected endoscopically with apparent complete removal.

Two years later, the patient's symptoms had recurred and bronchoscopy had been repeated. A small recurrent polypoid carcinoid had been removed. Thoracotomy had been advised and the patient had been referred to the Mayo Clinic for additional consultation.

At that time the results of physical examination and thoracic roentgenography were normal. Bronchoscopic examination revealed a small polypoid projection on the lateral wall of the intermediate bronchus, 4 mm. distal to the orifice of the right upper lobe, and biopsy of this projection showed a small focus of carcinoid tissue.



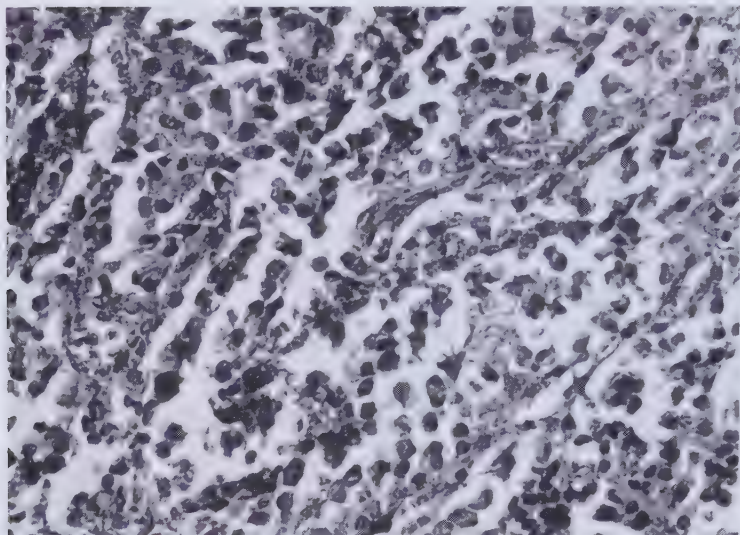


Figure 5 (Case 3). Section of carcinoid tumor removed endoscopically (hematoxylin and eosin; $\times 350$).

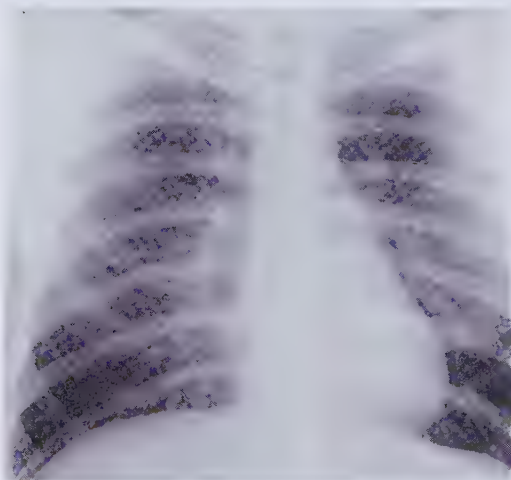


Figure 6 (Case 3). Thoracic roentgenogram two years after endoscopic removal of recurrent tumor and thoracotomy: normal appearance.

Because the tumor was recurrent, thoracotomy was advised again. The operation disclosed no abnormality of the parenchyma of the lung, the bronchi, or the lymph nodes; and therefore pulmonary resection was not done. Instead, the base of the tumor pedicle was fulgurated transbronchoscopically.

The patient has had two yearly follow-up examinations. On each occasion physical, roentgenographic, and bronchoscopic findings were entirely normal (Fig. 6).

The typical bronchial carcinoid, because it grows both endobronchially and extrabronchially, is best treated by thoracotomy and pulmonary resection. The majority of carcinoids that are entirely endobronchial

should be treated the same way, since chronic bronchial obstruction usually leads to bronchiectasis, suppuration, and pulmonary fibrosis distal to the tumor. In the case just presented, pulmonary resection was not performed because no residual tumor could be found at thoracotomy. However, in that case and in all cases treated transbronchoscopically, regular recheck examinations including bronchoscopy are indicated because of the possibility of recurrence of the tumor.

Multicentric Carcinoid Tumor

Multiple primary bronchial carcinoids, involving one lung or both, are extremely rare. Felton and associates have described two such cases, and others have been reported by Kay and by Umiker and Storey. Multiple cylindromatous tumors of the lung invariably are found to be metastatic, the primary tumor originating elsewhere in the lung or in another location (salivary gland, and so on).⁹

One case of multicentric bronchial carcinoid (reported previously²⁴) has been observed at the Mayo Clinic.

CASE 4. A 57-year-old woman came to the Mayo Clinic because of a chronic, moderately productive cough and recent nocturnal choking. A roentgenogram of the thorax revealed a density low in the left lung, suggesting pneumonitis (Fig. 7, *a*). Results from studies of the sputum for acid-fast bacilli, fungi, and cancer cells were negative, as were the findings on bronchoscopic examination. The pulmonary density subsequently cleared.

The patient returned to the clinic four years later with rheumatoid arthritis. On this occasion the thoracic roentgenogram showed nodular densities in the periphery of both lungs (Fig. 7, *b*). Again the findings from studies of the sputum were negative. The nodular densities were thought to be granulomas and observation was advised.

The patient returned again two years later, at the age of 63, because a thoracic roentgenogram made in her home community had shown enlargement of the nodular pulmonary densities, especially in the region of the right middle lobe. The cough had persisted and she had noted exertional dyspnea, hoarseness, and some wheezing. No diarrhea or cutaneous flushing had occurred, and no edema or heart murmurs were noted. Roentgenographic examination at this clinic confirmed the enlargement of the pulmonary nodules (Fig. 7, *c* and *d*).

Right thoracotomy was performed and multiple carcinoid adenomas were found in the middle and lower lobes. Hilar lymph nodes were not involved. The middle and lower lobes were resected (Fig. 8, *a*). Two carcinoids were analyzed for serotonin content, and the concentration in each was abnormally high (86 mcg./gm. of tumor tissue in one and 62 in the other, as opposed to a probable normal tissue concentration of less than 5)²². The urinary concentration of 5-hydroxyindoleacetic acid was normal postoperatively.

The patient did well for a week following operation but then developed shock and died despite vigorous therapy. At necropsy the cause of death was found to be thrombosis of the portal vein with hemorrhagic infarction of the bowel and severe congestion of the liver. Multiple carcinoid tumors were found in the left lung and the upper lobe of the right (Fig. 8, *b*). There was no evidence of nodal or hepatic metastasis. No carcinoid tumor was found in the gastrointestinal tract and there was no valvular heart disease.

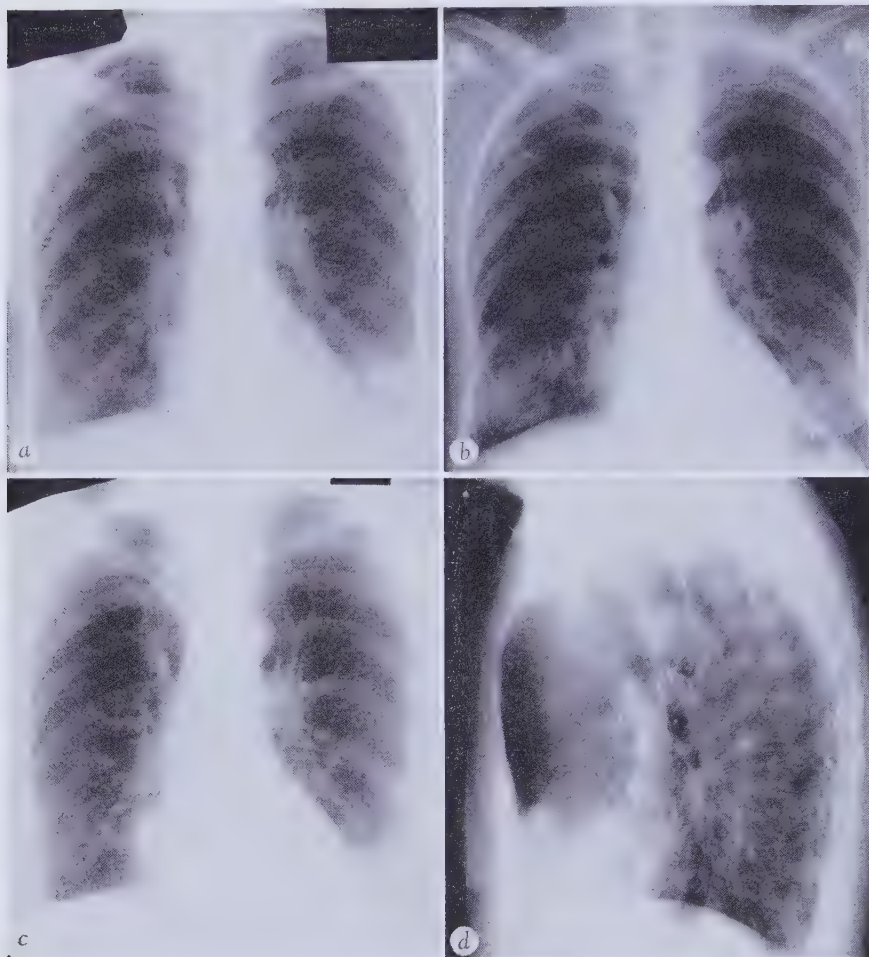


Figure 7 (Case 4). Multicentric bronchial carcinoids. *a*, Density suggesting pneumonitis in left pulmonary base. *b*, Four years after *a*: bilateral multiple peripheral nodular densities. *c* and *d*, Preoperative, two years after *b*: nodular densities on right have enlarged (best seen in *d*).

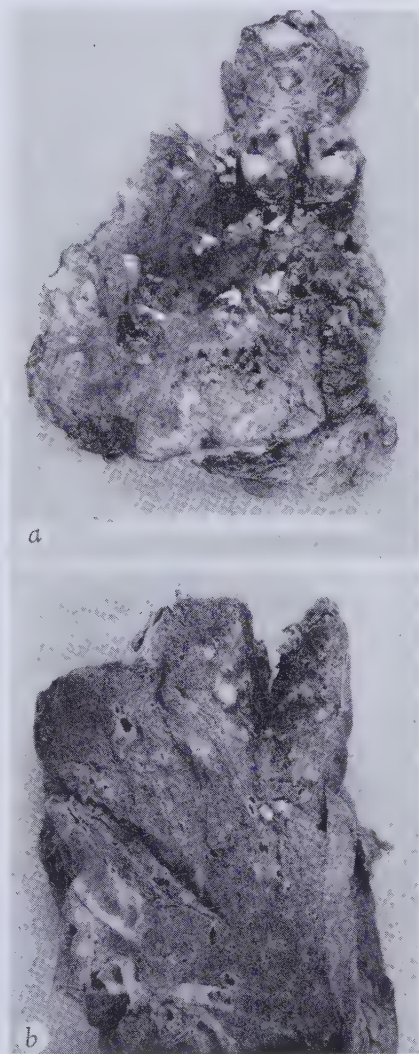
This case is very similar to those examples of multiple primary bronchial carcinoids reported by others.^{9, 16} The absence of metastasis to hilar lymph nodes or liver and the failure to find another carcinoid tumor elsewhere seem to establish the diagnosis of multicentric adenoma beyond reasonable doubt.

The patient had experienced dyspnea and wheezing but none of the other features of the carcinoid syndrome (cutaneous flushing, diarrhea, edema, valvular heart disease, and so on). Serotonin, of which the two tumors removed from this patient at operation contained abnormally high concentrations, has been implicated in the carcinoid syndrome. However,

it has been shown that there is no direct relationship between the concentration of serotonin in carcinoid tumors and the presence or absence of the syndrome.^{5, 11}

At the Mayo Clinic, elevated concentrations of serotonin were found in the tissue of 9 of 16 bronchial carcinoids analyzed for this substance. Levels were extremely variable, ranging up to 476 mcg./gm. of tumor tissue. None of the tumors analyzed was associated with the carcinoid syndrome. Serotonin concentrations in bronchial carcinoids tended to be considerably lower than those observed in carcinoid tumors of the small intestine.¹¹

Figure 8 (Case 4). *a*, Operative specimen: middle and lower lobes right lung, showing carcinoid tumor. *b*, Necropsy specimen: left lung, showing multiple carcinoid tumors.



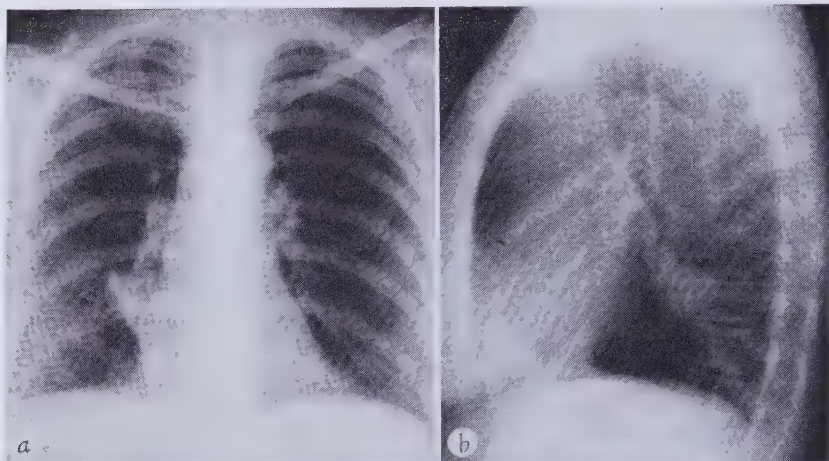


Figure 9 (Case 5). Bronchial carcinoid and carcinoid syndrome. *a* and *b*, Rounded density in right lung before resection of primary pulmonary tumor.

Bronchial Carcinoid Associated With Carcinoid Syndrome

The carcinoid syndrome is a well-defined clinical entity. As already noted, there are cutaneous, cardiovascular, gastrointestinal, and respiratory manifestations. The syndrome rarely occurs unless the primary carcinoid tumor has metastasized. Characteristically, the liver is involved and is markedly enlarged. The syndrome was first described in association with carcinoid tumors of the small intestine, but it also has been encountered in a number of patients with bronchial adenomas of the carcinoid type. Five such cases have been seen at the Mayo Clinic. One of these, reported in detail and illustrated in an earlier issue of this publication,⁷ is summarized briefly here.

CASE 5. A 52-year-old woman in apparent good health had had a mobile-unit survey roentgenogram of the thorax which disclosed a rounded density in the right lung, confirmed by standard roentgenograms taken a short time later (Fig. 9, *a* and *b*). At thoracotomy a bronchial adenoma of the carcinoid type had been found. Since this had involved the superior segment of the right lower lobe, and had metastasized to the hilar lymph nodes, pneumonectomy had been performed.

The patient had remained well for 15 months but then had developed abdominal pain, episodic diarrhea, flushing, and dyspnea. Subsequently she was referred to the Mayo Clinic, where physical examination revealed a marked enlargement and nodularity of the liver. No heart murmur or edema was present. Episodes of facial flushing and urticaria were observed. Studies of the urine for 5-hydroxyindoleacetic acid gave abnormally high values (10 and 35 mcg./24 hr., in contrast to a normal value of less than 10).²⁸

Laparotomy revealed massive involvement of the liver by metastatic carcinoid tissue (Fig. 10). The intestine and mesentery were normal.

The patient died of metastatic carcinoid tumor a year later. Permission for necropsy was not granted.

At the Mayo Clinic, the carcinoid syndrome has appeared in 2 per

cent of those patients with bronchial carcinoids who were treated by pulmonary resection²⁰ and in 7 per cent of a series of patients with proved carcinoid of the small intestine.¹⁹

Some interesting correlations have been made between the histology of carcinoid tumors and their biochemical and pathologic behavior. Davis and Kennedy found that carcinoid tissue with a high serotonin concentration tended to be unusually pleomorphic with relatively undifferentiated, hyperchromatic cells. Parshall and associates observed a similar histologic configuration rather frequently among bronchial carcinoids that had metastasized. In the case of bronchial adenoma with carcinoid syndrome summarized above, the pathologist commented on the unusual degree of hyperchromatism and cellular activity of the tumor tissue.⁷

One is tempted to conclude that the relatively undifferentiated bronchial carcinoid is the most likely to have a high concentration of serotonin, to undergo metastasis, and to be associated with the carcinoid syndrome. Yet it is difficult to reconcile such a conclusion with the previously noted lack of correlation between the serotonin concentration in carcinoid tumor tissue and the occurrence of the carcinoid syndrome.^{5, 11}

Bronchial Carcinoid Associated With Endocrine Disorders

Cushing's syndrome and neoplastic disease—particularly of the thymus, pancreas, or lung—occur together more frequently than can be accounted for by chance.²³ The association of Cushing's syndrome and bronchogenic carcinoma, especially small-cell carcinoma, has received considerable attention lately.^{2, 23, 31} It has been shown that the pulmonary tumor may at times produce corticotropin-like substances.²⁵

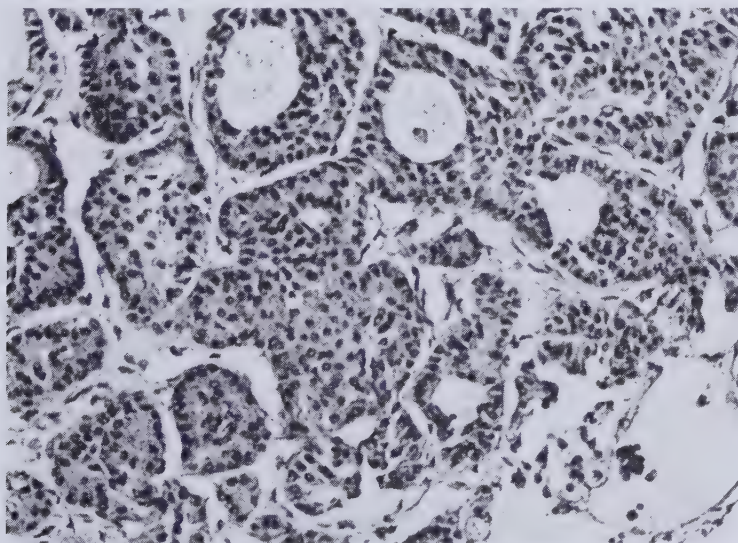


Figure 10 (Case 5). Section of hepatic metastatic lesion (hematoxylin and eosin; $\times 200$).

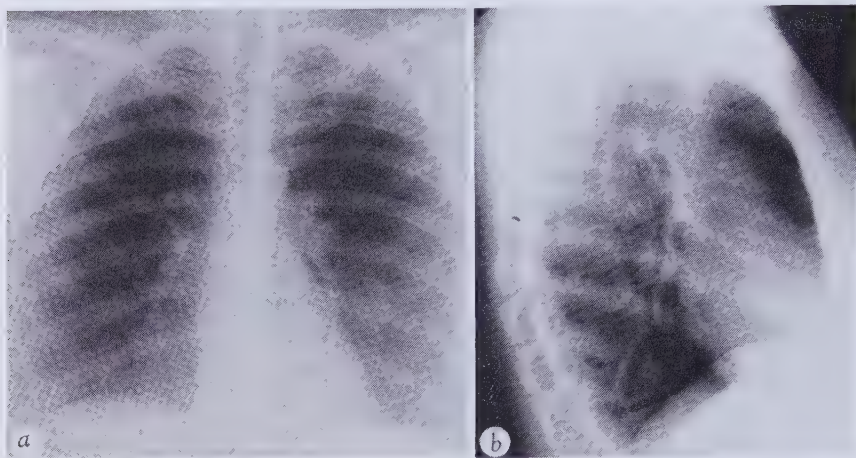


Figure 11 (Case 6). Bronchial carcinoid and previous Cushing's syndrome. *a* and *b*, Tumor appears as solitary circumscribed peripheral density in left lung.

Bronchial carcinoid and Cushing's syndrome have occurred in the same patient often enough to suggest something more than coincidental association. Five such cases have appeared in the literature,^{3, 4, 8, 23} including one from the Mayo Clinic.²³ In each instance the adenoma was of the carcinoid type. In one case the carcinoid syndrome also appeared.⁸

CASE 6. A 42-year-old woman had been seen at the Mayo Clinic repeatedly between the ages of 32 and 40 years for treatment of Cushing's syndrome secondary to bilateral adrenal cortical hyperplasia. Resection of adrenal tissue had been performed three times, and two courses of pituitary radiation had been given. During all of this time repeated roentgenographic examinations of the thorax disclosed no abnormality. Following the third operation there was a remission of Cushing's syndrome.

The patient returned two years later for a recheck examination. No evidence of recurrent Cushing's syndrome was found, but thoracic roentgenograms revealed a small solitary circumscribed nodule in the periphery of the left lung (Fig. 11, *a* and *b*). The nodule was resected at thoracotomy and proved to be a bronchial carcinoid. Lymph nodes were not involved.

Three years later, at the patient's most recent follow-up examination, there was no evidence of recurrence of either Cushing's syndrome or the bronchial adenoma.

Bronchial adenomas of the carcinoid type have been observed in association with other endocrine disorders also. There are published accounts of four cases of bronchial carcinoid associated with acromegaly.^{1, 15, 26, 32} Three cases of bronchial carcinoid and multiple endocrine adenomas have been reported,^{13, 30, 33} including one from the Mayo Clinic.³⁰

These observations suggest that a more than casual relationship exists between carcinoid tumors of the bronchus and certain endocrinopathies. The nature of this relationship becomes more intriguing when one considers that the carcinoid tissue of the body is regarded by some as a diffuse endocrine organ.^{10, 14}

SUMMARY

The current classification of tumors of the bronchus of mucous-gland origin is presented along with those features which seem to justify the breakdown of this group into four distinct pathologic and clinical entities. Certain uncommon manifestations of bronchial carcinoid have been described.

Endobronchial carcinoids may produce symptoms suggesting asthma or bronchitis, and may not be visualized on a standard thoracic roentgenogram. Inspiration-expiration roentgenograms, fluoroscopy, tomography, and bronchoscopy are valuable diagnostic aids.

Multicentric bronchial carcinoids are extremely rare. Because of their peripheral location and slow rate of growth, they may be mistaken for multiple pulmonary granulomas. Lung biopsy may be required to establish the correct diagnosis.

Bronchial carcinoids may produce serotonin and may be associated with the carcinoid syndrome. They may also be associated with certain endocrinopathies, notably Cushing's syndrome, acromegaly, and pleuri-glandular adenomatosis. If there is evidence of a pulmonary tumor in a patient with either the carcinoid syndrome or an endocrine disorder, bronchial adenoma of the carcinoid type should be considered.

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Management of Pleural Effusions

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Accumulation of an abnormal quantity of fluid in the pleural space is a common medical problem. Normally a small amount of fluid is present, serving as a lubricant for the pleural surfaces. Little is known about the precise mechanism of formation and absorption of normal pleural fluid or its composition.

NATURE OF PLEURAL EFFUSION

A pleural effusion may be either a transudate or an exudate. Transudates may result from increased venous pressure, as in congestive heart failure, or from venous obstruction, as when the azygos vein is invaded by a malignant neoplasm. A transudate also may be produced by hypoproteinemia, regardless of its cause. In our experience, cirrhosis of the liver and chronic renal disease have been the usual diseases responsible for such a syndrome. Pleural exudates may be caused by a wide variety of diseases: infectious, neoplastic, and miscellaneous as discussed in greater detail below. It is assumed that the exudation is due to inflammation of the pleural membranes with formation of pleural fluid at a rate which exceeds the rate of its resorption. In some instances at least, the disease itself may cause this rate of resorption to be reduced below normal.

Unfortunately, little is known about the pathologic physiology of pleural effusion. Clauss, Yacoubian, and Barker studied the dynamics of pleural effusions, using deuterium oxide injected either intrapleurally or intravenously. They found a high rate of pleural fluid turnover (30 to 75 per cent per hour) without any relation to the size of the effusion or the underlying disease. Similar studies at the Mayo Clinic gave similar results, but with a greater spread in the rates of turnover (12 to 100 per cent per hour).

Pleural effusion may be associated with certain diseases affecting primarily the region below the diaphragm. It seems likely that in these cases fluid passes from the peritoneal cavity through lymphatics into the pleural space. Meigs' syndrome (pleural effusion with ovarian tumor—usually a fibroma) is the classic example of this. Pleural effusions associated with acute pancreatitis and subdiaphragmatic abscess also may have this pathogenesis, at least in part. In addition in these diseases the inflammation itself may spread through the diaphragm and cause an actual pleural exudation. Obviously, more knowledge is needed before we can thoroughly understand the formation of pleural effusions and their management.

Etiology

As indicated by the foregoing discussion, pleural effusion may be associated with many different diseases. These may be classified in various ways. The classification in Table 1 has been helpful to us. It is obvious that the effusion is seldom the primary disease, even though it may be responsible for the patient's symptoms and the more readily apparent signs of disease. The basic cause must be determined in each case if this is possible, for proper treatment usually is the treatment of the underlying disease.

Table 1. Causes of Pleural Effusion

I. Neoplasms	IV. Miscellaneous
A. Pleural, primary	A. Transudates
1. Benign fibrous mesothelioma	1. Cirrhosis of liver
2. Diffuse malignant mesothelioma	2. Chronic nephrosis
B. Pleural, secondary	B. Exudates
1. Bronchogenic carcinoma	1. Pulmonary
2. Carcinoma of breast	a. Pulmonary infarct
3. Lymphomas	b. Sterile effusion with pneumonia
4. Miscellaneous primary neoplasms	c. Loeffler's syndrome
II. Congestive Heart Failure	d. Sarcoidosis
III. Infections	2. Extrapulmonary but thoracic
A. Viral	a. Trauma to chest wall
B. Bacterial (including tuberculosis)	b. Spontaneous hemopneumothorax
C. Fungal	c. Pneumothorax
D. Protozoal	3. Subdiaphragmatic
	a. Subdiaphragmatic abscess
	b. Acute pancreatitis
	c. Meigs' syndrome
	4. Systemic diseases
	a. Lupus erythematosus
	b. Rheumatoid arthritis
	c. Periarteritis nodosa

DIAGNOSIS

Symptoms

A pleural effusion may be asymptomatic until the quantity of fluid increases enough to cause dyspnea and a constant tightness or a pressure in the chest. Sharp pleuritic pain may be present at the onset of the pleurisy, being replaced by a dull ache when the effusion separates the visceral pleura from the parietal pleura. The pain of pleurisy may be very severe and is usually accentuated by any action that moves the visceral pleura over the parietal pleura, such as breathing or coughing. The location of the pain is dependent on the location of the pleurisy and varies from the shoulder to any part of the chest wall to the epigastrium. The pain may inhibit respiration and cause dyspnea before there is enough effusion to interfere with the respiratory function. Cough may develop, but it probably is due to the underlying pulmonary disease or the collapse of the affected lung rather than to the pleural effusion itself. Fever may be present, especially when the underlying disease is an infection or is complicated by an infection. Many other systemic symptoms may be present, depending on the basic disease that is causing the effusion.

Physical Signs

Small amounts of fluid may not be detected on physical examination. When the quantity is sufficient, the typical physical signs are decrease in motion of the affected side of the thorax, diminution of tactile fremitus, flatness on percussion, and absence of breath sounds. In some instances, perhaps because the fluid is under increased pressure, the breath sounds come through loud and clear.

Roentgenographic Evidence

Small amounts of fluid may not be visualized in routine x-ray examinations of the thorax. When the quantity of fluid is greater, it usually accumulates first in the most dependent place, thus causing obliteration of the costophrenic sinus on the roentgenograms. The presence of fluid in such cases can be proved by taking films with the patient lying on the affected side (Fig. 1). Larger quantities of fluid result in the typical roentgenographic appearance of effusion (Fig. 2). When air also is present in the pleural space, the characteristic "air-fluid" level is seen (Fig. 3).

Atypical pictures are not uncommon. Large quantities of fluid may accumulate between the inferior surface of the lung and the diaphragm (Fig. 4). Loculations of fluid may occur anywhere in the pleural space—anteriorly, posteriorly, laterally, superiorly, mediastinally, or in any of the fissures—depending on the quantity of fluid and the location of the adhesions responsible for the loculation (Fig. 5).

Some interlobar collections may have the roentgenographic appearance

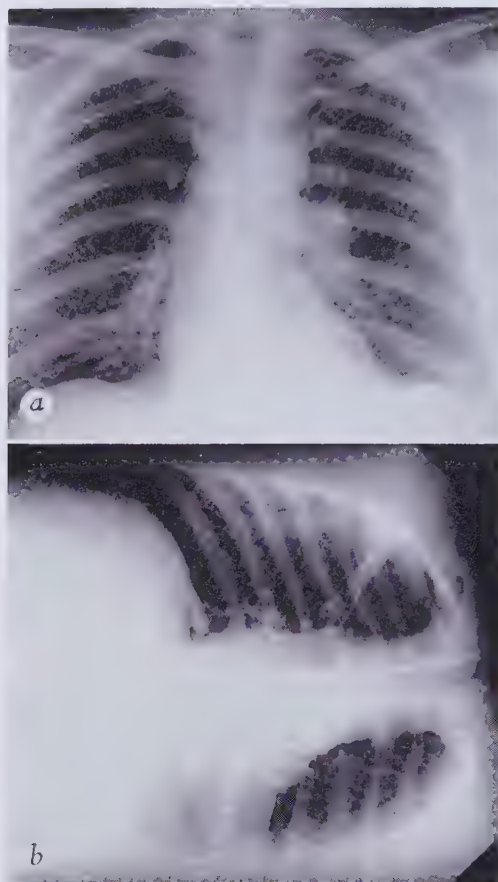


Figure 1. Effusion of small quantity. *a*, Standard thoracic roentgenogram showing obliteration of left costophrenic angle. *b* (Same case), Left lateral decubitus film showing layering of fluid in dependent portion of thorax.



Figure 2. More copious effusion. Typical roentgenographic appearance of fluid in both pleural spaces. Note density on left side extends up along lateral chest wall.

Figure 3. Typical roentgenographic shadow of fluid and air filling right pleural space.

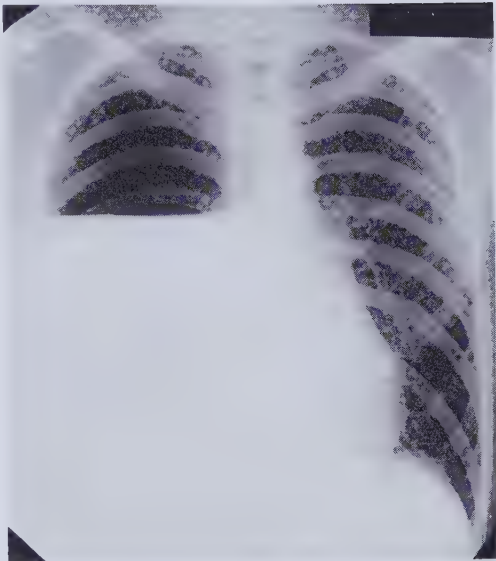


Figure 4. Fluid between diaphragm and lung. *a*, Apparent elevation of right diaphragm. *b* (Same case), Right lateral decubitus film taken same day, showing large amount of fluid.

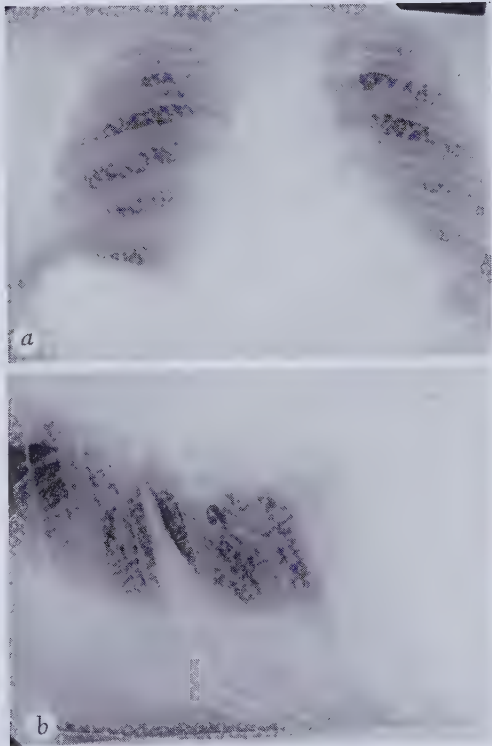
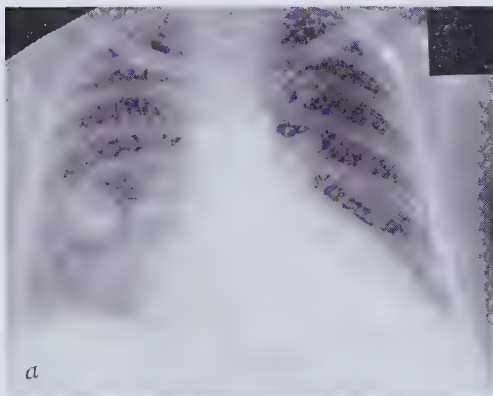




Figure 5. Unusual loculation of pleural effusion in lateral and superior portion of left hemithorax.



PA
and

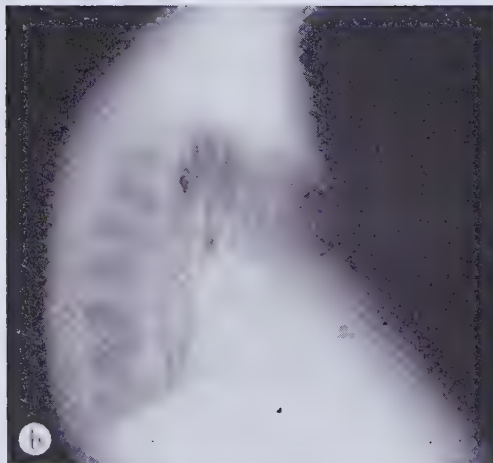


Figure 6. Congestive heart failure and pocket of fluid in fissure between middle and upper lobes of right lung. Shadow disappeared during effective therapy for congestive heart failure. a, Posteroanterior view. b, Lateral view, showing extension of fluid into fissures.

Lateral

of a tumor (Fig. 6). It is remarkable that this phenomenon has been observed only in association with congestive heart failure. Since the shadow disappears with treatment of the cardiac disease, it has been aptly called "vanishing tumor."

Examination of the Fluid

Most patients with pleural effusion should have a thoracentesis, so that the fluid may be examined thoroughly in the laboratory. In many instances this will yield the only evidence on which to make a diagnosis.

The proper technique of thoracentesis is given in the standard texts. It is not a simple procedure to be delegated casually to a neophyte. A careful preoperative examination including special roentgenographic studies as needed should be conducted to make certain that there is a pleural effusion and to localize it accurately. If this is done, a specimen of fluid adequate for various laboratory examinations can almost always be obtained.

The gross appearance of the fluid is always of interest and enables one to classify the fluid as serous, purulent, bloody, or milky. However, this gives only a hint as to possible causes of the effusion, and other examinations are always needed.

Often counts of erythrocytes and of leukocytes and their differential in pleural fluid are made, but we have not found them to be of any clinical value and do not recommend them routinely.

Specific gravity of the fluid has been used widely to separate transudates from exudates, 1.016 being the generally accepted dividing point. In our experience, measurement of the concentration of protein has been more satisfactory, with 3.0 gm./100 ml. the dividing point.⁴ Figure 7 shows the accuracy of this measurement in separating transudates associated with congestive heart failure from exudates associated with tuberculosis and malignant disease.

For many years it has been known that in some cases of tuberculous effusion and some of empyema the concentration of glucose in pleural fluid was less than the concentration in blood.² Remarkably small concentrations of glucose have been found to be characteristic of pleural effusions associated with rheumatoid arthritis.³ Three Mayo Clinic patients with malignant disease and effusion had very low concentrations of glucose in the pleural fluid. Two of them had diffuse mesotheliomas of the pleura with effusion, and their glucose concentrations were 0 and 12 mg./100 ml. of pleural fluid. In the third, with alveolar-cell carcinoma and effusion, it was less than 5 mg. Obviously the concentration of glucose is of interest but not of much help in establishing a diagnosis.

A pleural effusion is designated chylothorax when the concentration of fat is greater than 400 mg./100 ml. of fluid. As chylothorax is said to be associated usually with tumor, trauma, or tuberculosis, the chylous nature of the fluid may stimulate the clinician to search promptly for one of these causes for the effusion.

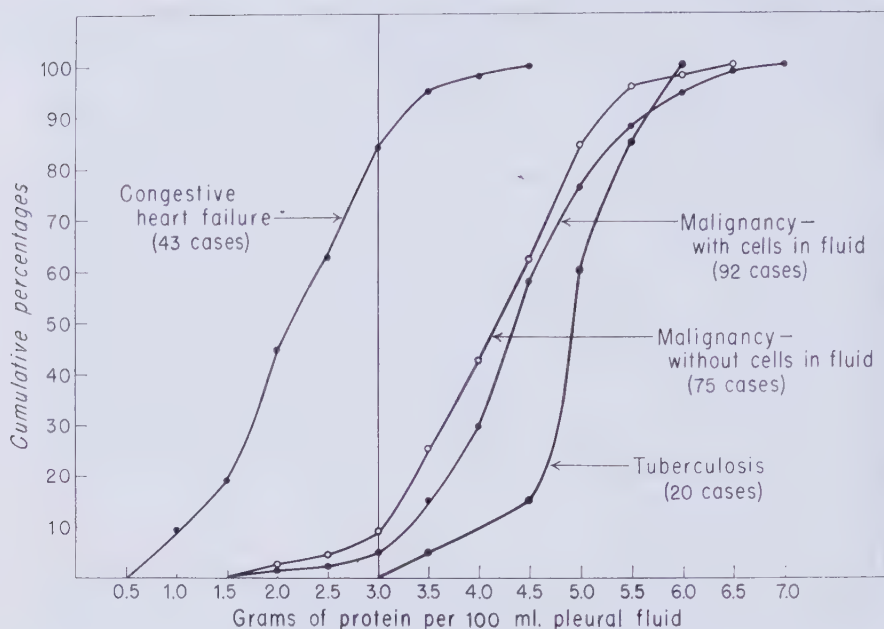


Figure 7. Cumulative-distribution curves, showing value of measurements of pleural-fluid protein in differentiating transudates from exudates. (From Carr, D. T., and Power, M. H.: Clinical value of measurements of concentration of protein in pleural fluid. *New England J. Med.* 259: 926-927 [Nov. 6] 1958. By permission of The Massachusetts Medical Society.)

Increase in lactic dehydrogenase activity in the pleural fluid is usually associated with effusions due to malignant neoplasm metastasizing to the pleural membrane.¹⁹ Amylase activity in the pleural fluid has been reported as increased in effusions secondary to acute pancreatitis.¹⁰

Bacteriologic examination of the fluid is of special value and should be carried out on all fluids aspirated for diagnostic study. Cultures for general pyogens and for acid-fast bacilli should be routine. Although fungal infections are not common causes of pleural effusion, the possibility should be kept in mind so that the fluid will be cultured for fungi in appropriate cases. In some laboratories inoculation of an animal with the fluid is preferred to culture of it for acid-fast bacilli.

A portion of the fluid should always be sent to the cytologist for examination for malignant cells. In our experience about 50 per cent of pleural effusions due to malignant disease contain malignant cells. In some cases, the failure to detect malignant cells may be due to the fact that the effusion is caused by obstructive pneumonitis secondary to a carcinoma rather than by actual spread of the neoplasm to the pleural membrane. Mesothelial cells may be confused with malignant cells, and this is said to cause false-positive reports. A review of our records, however, revealed only 3.3 per cent false-positive reports in a series of 450 patients examined during the years 1950 through 1959.⁹

Pleural Biopsy

If careful examination of the pleural fluid fails to establish an etiologic diagnosis, pleural biopsy becomes necessary so that proper therapy may be instituted. Pleural biopsy may be performed either by the use of a specially designed needle or by open thoracotomy. A variety of special biopsy needles have been developed, including the Silverman needle,¹⁷ the Cope needle,⁶ and the Harefield needle.¹ All have been used with success in the diagnosis of indeterminate pleural disease; but in a recent report comparing the results between the Silverman needle and the Harefield needle, the superiority of the latter was clearly demonstrated.¹⁴ Though somewhat similar to the Cope needle, the Harefield needle has some advantages over it, for it allows aspiration of fluid at the time of pleural biopsy and allows resection of a specimen of tissue including intercostal muscles and adjoining pleura approximately 3 to 4 mm. in diameter, which is suitable for histologic study.

Considerable experience with the use of this needle has been reported from England, where it has been found successful in providing material for obtaining a positive diagnosis in approximately three quarters of the cases of tuberculous pleural effusion and two thirds of the cases of malignant pleural effusion.^{11, 15} We have found the needle particularly helpful

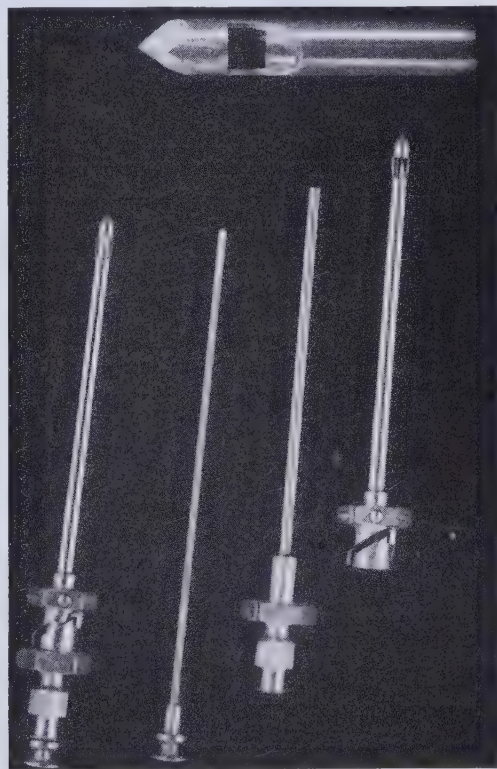


Figure 8. Harefield pleural punch biopsy needle. Completely assembled unit (below, left) is 13.5 cm. long. Components (toward right): stylet, inner cutting cylinder, and outer trocar tube. Magnified (above) is tip of trocar tube with notch partially closed by cutting cylinder.

in diagnosis of pleural disease and have employed it in preference to the others mentioned above, but have restricted its use to patients with pleural effusion.

The needle consists of two concentric tubes and a stylet (Fig. 8). The outer tube has a sharp trocar tip which will not puncture the lung. Just proximal to the tip is a deep notch which can be closed by twisting the hexagonal grip of the inner tube in a clockwise direction, thus advancing a sharp-edged cylinder past the notch and cutting off any tissue engaged within the notch. With the patient seated, an appropriate spot is chosen and infiltrated with a local anesthetic. To facilitate introduction of the trocar, a small incision is made in the skin with a scalpel. The instrument is inserted with the notch closed and carefully advanced into the pleural space as if for thoracentesis. The pleural fluid may be aspirated at this stage. For biopsy, the tube with the notch open is withdrawn while lateral pressure is applied in the direction of the notch, which is indicated by the small rounded knob on the hub of the needle. A catch is felt as the notch becomes engaged on the parietal pleura. The inner cutting core is advanced, obtaining the specimen, and the needle is then withdrawn.

Typical examples of biopsy specimens obtained by this method are shown in Figures 9 and 10.

If the diagnosis remains uncertain after examination of the tissue removed by the Harefield needle, pleural biopsy by open thoracotomy should be carried out. We prefer to use general anesthesia and employ a short lateral incision on the involved side. This is deepened to the intercostal muscle, which is divided to expose the parietal pleura; and a generous portion of that is excised. Part of the tissue thus obtained can be sent for bacteriologic examination and the remainder is examined histologically. Following such a procedure, the fluid is aspirated; the wound is closed in layers; and a small intercostal catheter is inserted for temporary drainage. Not only does this keep the pleural space empty and the lung expanded, thus encouraging pleural symphysis, but it facilitates the introduction of chemotherapeutic agents should they prove desirable. Usually the patient is ready for dismissal by the third or fourth day after operation.

Other Diagnostic Tests

As pleural effusions may be due to such a wide variety of diseases, diagnostic tests other than those on the fluid and the pleural membranes may be needed to help discover the cause of the effusion.

Pleural effusion is commonly associated with pulmonary disease, and careful investigation of the lungs may lead to a correct diagnosis. The roentgenograms that show the fluid may also show some evidence of a pulmonary lesion. In some cases the quantity of fluid may obscure one lung completely and hide the primary lesion. In such cases roentgenograms of the thorax made after aspiration of as much fluid as possible may be of great value. Thorough examination of the bronchopulmonary secretions

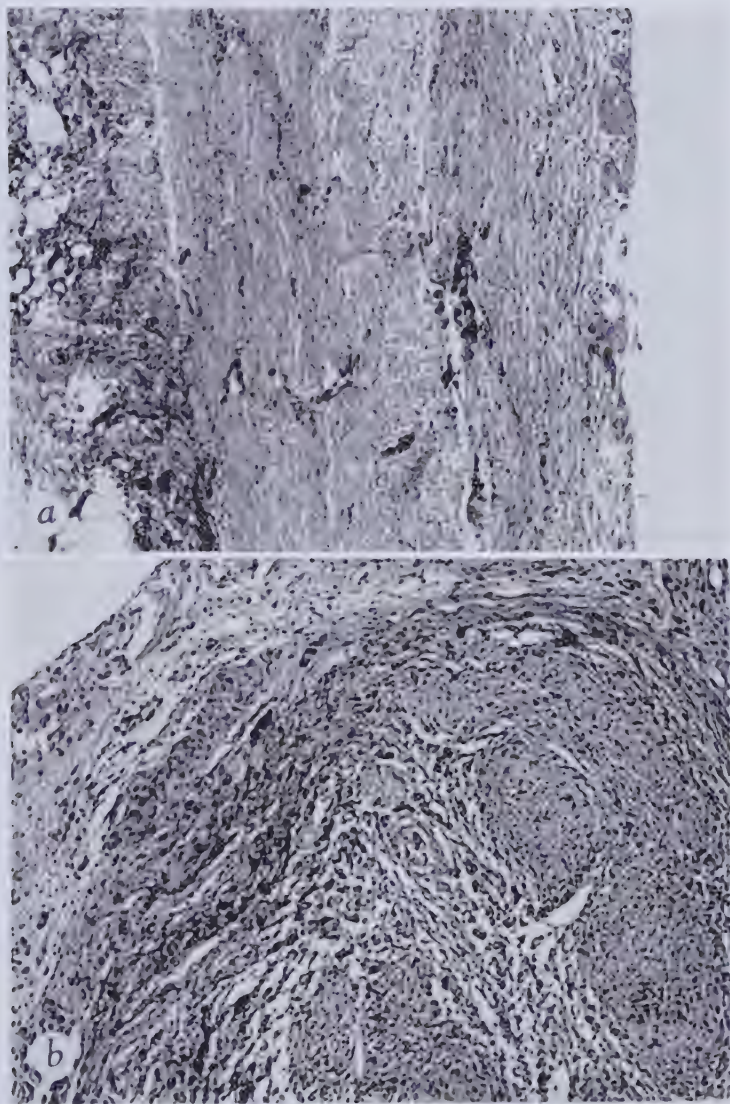


Figure 9. Biopsy specimens obtained with Harefield needle. *a*, Nonspecific inflammatory pleuritis. Portion of subpleural areolar connective tissue and pleura. Pleural surface is covered by thin layer of fibrin, and pleura shows moderate fibrous thickening. Scattered collections of lymphocytes in pleural and subpleural tissue. (Hematoxylin and eosin; $\times 80$.)

b, Granulomatous pleuritis. Noncaseous tubercle composed of histiocytes and scattered giant cells. Silver chromate and night blue stains were negative for fungi and acid-fast bacilli, but culture revealed *Mycobacterium tuberculosis*. Presumptive diagnosis of tuberculosis was made from histologic findings and chemotherapy was instituted prior to report on culture. (Hematoxylin and eosin; $\times 125$.)

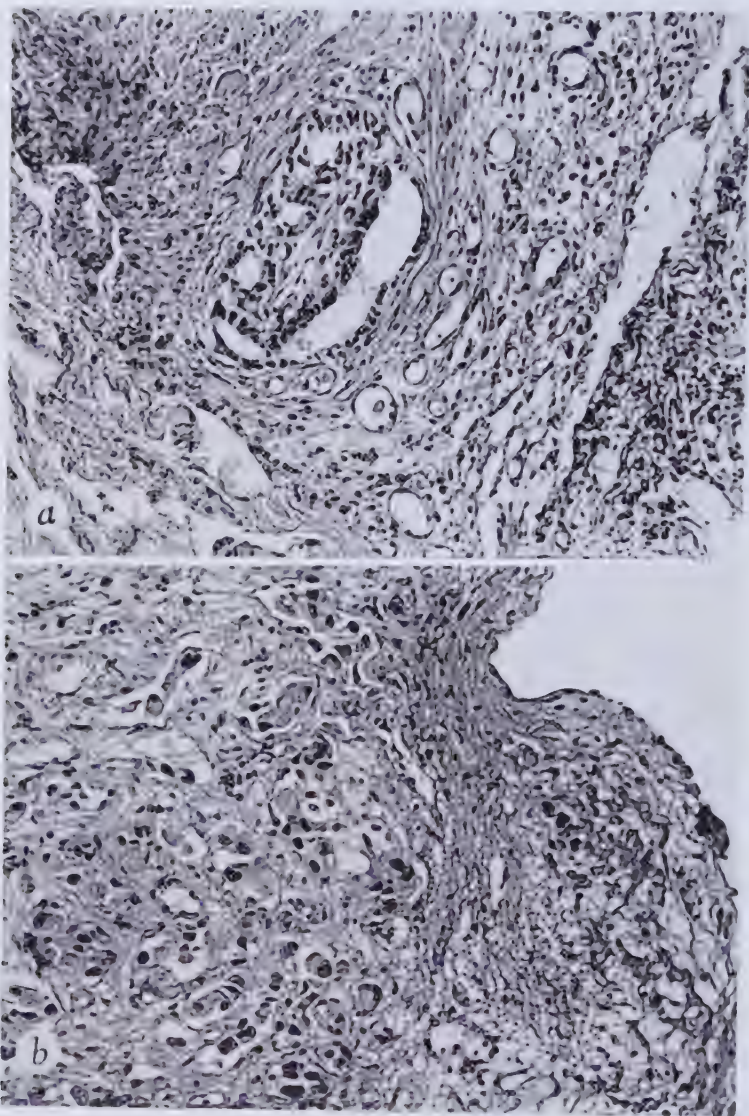


Figure 10. Biopsy specimens obtained with Harefield needle. *a*, Metastatic adenocarcinoma, well differentiated. Focus of adenocarcinoma deep in subpleural tissue and adjacent to intercostal muscle. In specific and nonspecific inflammatory pleuritis, proliferating mesothelial cells near pleural surface may be mistaken for metastatic adenocarcinoma. (Hematoxylin and eosin; $\times 165$.)

b, Metastatic adenocarcinoma, poorly differentiated. Diffuse infiltrate of carcinoma cells in pleura. Surface of pleura is covered with layer of fibrin and a few inflammatory cells. (Hematoxylin and eosin; $\times 165$.)

may be helpful, especially in establishing a diagnosis of tuberculosis or a malignant neoplasm as the underlying disease. This should be done, even though the patient has no spontaneous cough or expectoration; and it can be made possible through induction of sputum by inhalation of heated aerosols, or gastric intubation and aspiration, or aspiration of secretions at bronchoscopic examination.

The tuberculin test should be performed on all patients having pleural effusion without an obvious cause. A positive result in a patient whose reaction prior to effusion was negative should make one suspicious that the effusion is due to a recently acquired tuberculous infection. False-negative results may be obtained early in the course of the effusion and should not be used to exclude the possibility of tuberculosis as the cause, for a positive result may be obtained a few weeks later when the acute pleural reaction and fever have subsided.

Obviously a patient with pleural effusion should have a complete physical examination, and this may reveal clues that lead to the diagnosis. Likewise, appropriate examinations of the blood may yield clues that lead to some of the causes of pleural effusion listed in Table 1.

TREATMENT

Treatment of pleural effusion may be specific for the disease causing the effusion or directed at the effusion itself to relieve the patient of symptoms it causes.

Infectious diseases causing effusion obviously should be treated with appropriate antimicrobial agents. Tuberculous pleurisy with effusion is so important that it deserves special mention. Anti-tuberculosis drugs should be given in all cases whose connection with tuberculosis is either proved or probable. The benign appearance of the pleural disease is misleading, and the frequency of the development of progressive and serious tuberculosis of the lungs and other organs after a few years has been well documented.^{8, 16} Furthermore, many patients exhibiting tuberculous pleurisy with effusion already have serious pulmonary tuberculosis, the lesions being obscured in thoracic roentgenograms by the effusion. As these patients may be expectorating tubercle bacilli, they should—with very few exceptions—be admitted to a tuberculosis hospital for their treatment.

Effusions secondary to congestive heart failure usually respond satisfactorily to appropriate treatment for the heart failure. If a significant amount of fluid is present, it should be aspirated, as it may interfere with the patient's respiratory function. In some cases repeated aspiration of pleural fluid is necessary. Rarely, the pleural effusion persists after other manifestations of congestive heart failure have cleared, and thoracentesis is needed to relieve the patient of the residual fluid.

Pleural effusion due to metastatic lesions is characterized by a tendency to recur, and repeated aspirations of large amounts of fluid may be necessary for relief of symptoms caused by the fluid. Instillation of radioactive gold has been found to reduce or even prevent the accumulation of fluid in such cases.⁷ More recently the instillation of nitrogen mustard into the pleural space has been found equally efficacious.¹² In recent years we have inserted an intercostal tube into the pleural space 24 hours after the instillation of the nitrogen mustard. By attaching the tube to a suction pump we have attempted to keep the pleural space empty and the pleural membranes in contact with each other for two or three days, hoping to facilitate pleural adhesions and obliteration of the pleural space so that fluid could not reaccumulate. It is our clinical impression that this technique has improved the results of instilling nitrogen mustard into the pleural space.

Parietal pleurectomy has been recommended in the management of pleural effusion secondary to metastatic malignancy,¹³ but we have not used it.

Whatever the cause of the effusion, repeated aspiration may be needed if the fluid reaccumulates and causes the lung to collapse. Aspiration of the fluid is particularly urgent if it is bloody or has a high concentration of protein. If such fluid is left in the pleural space, fibrinous deposits on the visceral pleura may make the lung unexpandable and necessitate pleural decortication.

Diuretics may be helpful in slowing the accumulation of pleural fluid and decreasing or possibly eliminating the need for repeated thoracentesis, even with malignant effusion.¹⁸

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Pulmonary Embolism and Infarction

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Pulmonary embolism is the most common serious pulmonary disorder. More frequently a cause of death than pneumonia or bronchogenic carcinoma, it is believed to cause about 47,000 deaths annually—more than traffic accidents—and is a significant contributory cause in three times that number. Among necropsy cases it is the immediate cause of death in from 2 to 6 per cent.

It is well known that cardiac patients are likely to develop pulmonary embolism, and not surprising to learn that it is found at necropsy in a third of those who had cardiac disease and in nearly half of those who suffered from congestive failure.

One of every 500 surgical patients can be expected to die of pulmonary embolism, but it causes even more total deaths among medical patients. Modern preventive measures have proved helpful, and yet the frequency of pulmonary embolism has increased because of the greater aging of our population and our inclination to operate on more of these older people, for the incidence of embolism increases with age: it is rare under 20 years of age and unusual under 40. In regard to sex and race, there is no predilection.

Every medical practitioner knows all too well the treacherous nature of pulmonary embolism, which so often strikes without warning, causing death in a few minutes when it has been least expected. No branch of medical practice is completely free of this peril. Therefore, every physician should be alert to the possibility, aware of the warning it may give, and ready to administer treatment that often proves life-saving. It is hoped that better means of prevention and treatment will soon be forthcoming.

SOURCE OF EMBOLI

In about 90 per cent of cases, the sources of pulmonary emboli are the veins of the lower extremities, pelvis, and abdomen. Sometimes the

veins of the head, neck, and arms or the valves or wall of the heart are the sites of origin. Uncommonly the responsible embolic material may be malignant tumor cells, fat and bone marrow mobilized by trauma, amniotic fluid released during parturition, parasites, air from intravenous medications, or oil used in lymphangiography.

CAUSES OF THROMBO-EMBOLISM

Venous Thrombosis

In the veins, thrombosis is caused by local injury (inflammatory or traumatic), by slowing of the blood flow, or by increased clotting tendency of the blood.

Local injury to the vein may be caused by intravenous needles and medication, trauma, surgical procedures, and localized infection. Although these are frequent causes of thrombosis and thrombophlebitis, it is not so common for thrombi thus produced to shed emboli, because the inflammatory reaction usually binds the associated thrombi to the vascular wall. If thrombus formation extends well beyond the inflammatory segment, emboli may result. Most emboli originate in the larger and deeper veins, no significant number arising from superficial veins.

Slowing of venous blood flow results from immobility, bed rest, pressure on the extremity, and congestive heart failure. Stasis, rather than inflammation or increased coagulability, probably is responsible for most cases of embolism in medical patients and in those who have undergone childbirth, injury, or operation.

Increased coagulability of blood seems a logical cause of thrombosis, but its direct relationship is difficult to measure by available blood tests. It may well be a factor in postoperative thrombophlebitis and in cases of polycythemia vera or dehydration with hemoconcentration.

Perhaps it is best to consider many cases of thrombophlebitis and pulmonary embolism as idiopathic until their true nature is better understood. It is well known that thrombophlebitis—and therefore pulmonary embolism—is often associated with infectious disease, malignant disease, heart disease, blood dyscrasia, pregnancy, ischemia of an extremity, and various other conditions; but the reason for this association is generally obscure.

Intracardiac Thrombosis

Thrombosis within the heart is caused by slowing of the blood flow (auricular fibrillation, congestive heart failure, or eddies in a dilated chamber), or by damage to the endocardium (myocardial infarction, bacterial endocarditis). But even in patients with heart disease, embolism results more often from venous than from intracardiac thrombosis.

Pulmonary-Artery Thrombosis

Primary thrombosis of the pulmonary artery is rare but does occur.

PATHOLOGY

Emboli in the pulmonary arteries will proceed as far as their size permits. In about half of fatal cases, the main pulmonary artery at its bifurcation contains large coiled emboli; and in a fourth, both the right and left pulmonary arteries are obstructed. Among the rest, the occlusion involves a main pulmonary or lobar artery or multiple smaller vessels. Emboli are often present in the right atrium and ventricle and may seriously alter hemodynamics. With right ventricular failure, right atrial pressure may become greater than left. Right-to-left shunt then can occur through a patent foramen ovale, previously held closed by the greater left atrial pressure; and paradoxical embolism to the systemic circulation may result.

To cause death, obstruction of more than half—perhaps 85 per cent—of the pulmonary arterial circulation appears necessary. Occlusion of a single major branch seldom causes death in persons under 50 years of age. But factors in addition to occlusion of the pulmonary artery appear to be necessary. For example, death does not occur with occlusion of a main pulmonary artery during surgery, whereas it may if the vessel is obstructed by emboli. The cause of death in these instances is thought by some to be pulmonocoronary reflex and by others to be released serotonin.

Embolism without infarction produces little change in the lung tissue itself. It often causes dilatation of the pulmonary arteries, enlargement of the right ventricle and auricle, and the tissue alterations expected with congestive heart failure. Death from pulmonary embolism without infarction is common, but congestive failure or death rarely results from embolization of only smaller vessels of the lung.

Pulmonary infarction is present in only 50 to 60 per cent of cases of pulmonary embolism. Because of the double blood supply to pulmonary tissue (bronchial artery as well as pulmonary artery) and anastomosis in the pulmonary circulation itself, infarction is not likely to occur unless circulatory disease of the heart or lung compromises the bronchial as well as the pulmonary circulation. Infarcts of the lung are circumscribed, dark-red, consolidated lesions, frequently multiple. On microscopic examination the capillaries are seen to be congested and the alveoli are packed with blood cells. The hemorrhage apparently is due to necrosis, but necrosis seldom is so marked as with infarction of other tissues. Infrequently, necrosis with cavitation is seen. The infarct gradually resolves and heals with fibrosis, leaving little recognizable residual change as a rule.

It is unfortunate that an absolute diagnosis of pulmonary embolism

and infarction is not yet obtainable except by examination of tissue removed at operation (to be avoided if at all possible) or at necropsy. Perhaps the development of practical pulmonary arteriography will correct this situation.

PHYSIOLOGIC CONSIDERATIONS

Acute pulmonary embolism results in three major disorders of gas exchange: (1) arterial oxygen desaturation, which is associated commonly with embolism but uncommonly with the disorders often confused with embolism; (2) hyperventilation; and (3) differences in the CO_2 tension of arterial blood and end-expiration air. Normally CO_2 pressure is the same in arterial blood as in alveolar air. When pulmonary embolism involves a significant amount of lung, however, the P_{CO_2} of alveolar air (determined in end-expiration air) may be somewhat less than the P_{CO_2} of the arterial blood; and this has been advocated as a diagnostic test. Further study seems necessary to establish the validity and practicality of this means of diagnosing pulmonary embolism.

With acute obstruction of a major portion of the pulmonary arterial system, pulmonary hypertension develops in the proximal pulmonary artery and right ventricle; and this leads to right ventricular dilatation and failure. Reduced cardiac output in turn leads to systemic hypotension.

CLINICAL CONSIDERATIONS

Less than half of the necropsy-proved cases of fatal pulmonary embolism are recognized before death—a humiliating statistic.

Thrombophlebitis

On many occasions the recognition of thrombophlebitis is the clue to the diagnosis of pulmonary embolism. Unfortunately, when the source of the pulmonary embolus is a vein of the leg, thrombophlebitis can be detected in only half of the cases, and in perhaps half of these it does not appear until after the embolism.

Low-grade fever, especially after surgery, is often the only symptom. Pain and tenderness of the leg muscles, tenderness and induration of the vein, swelling of the leg and foot (unilateral or unequally bilateral), and positive Homans' sign (not diagnostic) are to be looked for.

Multiple episodes of thrombophlebitis can occur, but apparently each episode is self-limited: whether chronic thrombophlebitis exists is doubtful. When venous thrombosis develops, the clot is organized and adherent to the wall of the vein within eight to ten days as a rule, occasionally longer. Therefore the time during which emboli may be shed from an attack of

thrombophlebitis is probably limited. Thrombophlebitis and phlebothrombosis are probably different phases of the same entity and there is nothing to be gained by distinguishing between them.

Embolism Without Infarction

With prolonged rest in bed, pulmonary embolism may occur at any time—even after several weeks of rest. Embolism following injury or operation occurs during the second week in about half of the cases, and one-fourth of the time before and one-fourth after that week. It is unusual but can occur before the fourth day.

Often there are no symptoms or signs whatever. The first indication of trouble may come with exertion, such as getting out of bed, straining, or change of position. The patient may have a feeling of apprehension and may develop dyspnea, cyanosis, tachycardia, cough, fever, syncope, or convulsions. With obstruction of the main trunk or primary branches of the pulmonary artery, 20 per cent of the patients experience substernal or precordial pain that may extend to the shoulders and neck as in myocardial infarction. When these large emboli cause increase of pulmonary arterial pressure and acute cor pulmonale, the patient may have severe dyspnea (hyperventilation), cyanosis, circulatory collapse with drop in blood pressure, pallor, sweating, tachycardia, gallop rhythm or arrhythmias, and weakness of heart sounds. The pulmonic second sound may be louder than the aortic second sound. Venous pressure increases and the jugular veins become distended. With right-heart failure the liver soon becomes enlarged, tender, and painful and edema is noted. Rarely a pericardial friction rub is heard over the distended pulmonary artery; it may be confused with the pericardial rub of myocardial infarction.

Of patients with massive fatal pulmonary embolism, nearly half die within 15 minutes,² allowing little opportunity for life-saving treatment. Often the patient expires without any warning.

Infarction

Among clinically recognized cases of pulmonary embolism, infarction occurs in only 50 to 60 per cent. The infarction itself causes cough, hemoptysis, (in less than 25 per cent of cases), pleuritic pain (less than 50 per cent), pleural friction rub (less than 25 per cent), elevation of the diaphragm, and—over the region of the infarction—suppression of breath sounds and impairment of the percussion note. With involvement of the diaphragmatic pleura, abdominal pain and rigidity may suggest an acute abdominal condition. Occasionally icterus is associated with pulmonary infarction, further complicating the pattern. Icterus is rare in cardiac patients without pulmonary infarction. The development of bloody pleural fluid in small or large amounts is to be expected with infarction. It is unfortunate that little more than half of the patients with infarction will have some of these helpful diagnostic clinical signs or symptoms.

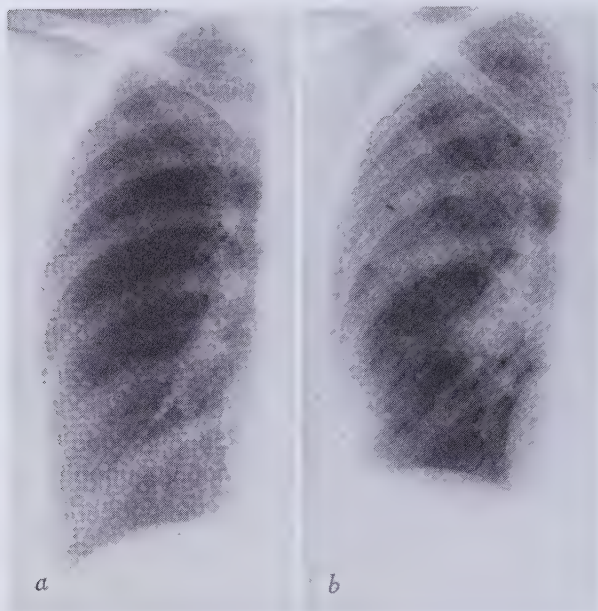


Figure 1. Course of pulmonary infarction following nephrectomy.

a, Immediately before right nephrectomy. Four days later, patient complained of pain in right lower portion of thorax.

b, Day following onset of symptoms. Enlargement of pulmonary artery in right hilar region indicates increased arterial pressure. Two infarcts: one in costophrenic angle, other at level of second anterior interspace.

LABORATORY AIDS TO DIAGNOSIS

Roentgenology

The roentgenologic diagnosis of pulmonary embolism and infarction is often difficult. Many patients, especially in the postoperative period, are bedfast and too ill to cooperate in making the best possible roentgenograms. This results in obscuration of anatomic detail by respiratory motion, in masking of pulmonary regions by the elevated diaphragm, or in changes in size and shape of the shadows of heart and major pulmonary arteries because of recumbent posture.

Pulmonary embolism does not always result in pulmonary infarction. It is wise, therefore, to consider the roentgenologic features of the two conditions separately.

PULMONARY EMBOLISM. In many instances of embolism no roentgenographic signs are produced, especially if the embolus is small and reaches a peripheral pulmonary artery or arteriole and does not produce an infarct. In a way, it is true also in the case of a massive embolus, for the patient dies suddenly before a roentgenologic examination can be obtained.

The signs that may be produced by an embolus are those relating to changes in physiology—in hemodynamics. The first of these is *enlargement*

of a major pulmonary artery or its large branches (Fig. 1, *a* and *b*). This is caused by an increase in pulmonary arterial pressure between the obstruction and the heart. For certainty of the presence of such enlargement, a roentgenogram made before the suspected embolic episode should be available for comparison. Even then it may be difficult to be sure if the post-embolic study is made at the bedside with the patient recumbent, a situation which always exaggerates the size of the hilar vessels.

A second sign, also related to an increase of pressure in the pulmonary arterial tree, is *enlargement of the right ventricle* and its outflow tract. This change in size and shape of the cardiac silhouette may be difficult to discern unless the patient can stand and cooperate in making roentgenograms of high quality.

Both of the two signs mentioned so far, being dependent upon pulmonary hypertension, may be evanescent. If the roentgenologic examination is not performed at the proper stage in the course of the embolic episode, they may not be seen at all.

A third sign, and one which has been extremely difficult for us to apply, is that first described by Westermarck. It consists of an absence or *paucity of vascular shadows* in the segment of the lung supplied by the occluded artery. There is some interest at present in attempting to develop this sign more fully by the use of venous angiocardiology or selective

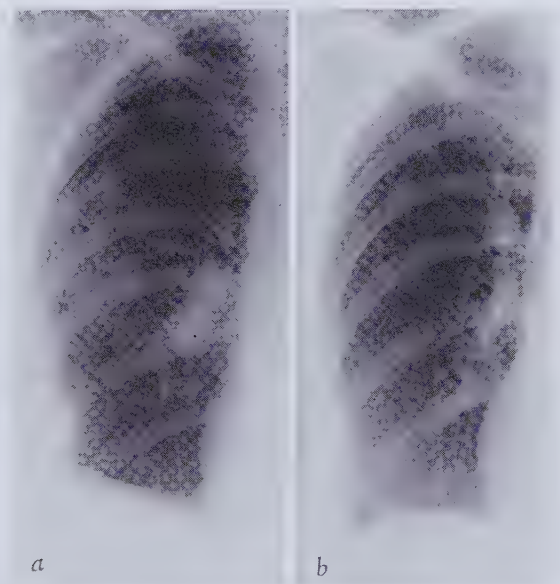


Figure 2 (same case as Fig. 1). *a*, Four days after Figure 1, *b*. Infarct in costophrenic angle is beginning to contract, as shown by elevation of adjacent part of diaphragm.

b, Six months after operation. Only small fibrous scar remains at site of lower infarct. Upper has healed by resolution, leaving no scar. Pulmonary artery in hilar region has returned to normal size.



Figure 3. Course of pulmonary infarction following surgery. *a*, Preoperative. *b*, First postoperative day. Patient experienced thoracic pain, cough, and hemoptysis. Roentgenogram shows slight enlargement of right pulmonary artery, elevation of right diaphragm, and slight clouding of cardiophrenic angle.



Figure 4 (same case as Fig. 3). *a* and *b*, Five days after embolic episode. Frontal and lateral projections showing well-developed wedge in posterior portion of right lower lobe.

right-heart or pulmonary arteriography. Perhaps the opacification of the pulmonary arterial tree by contrast material will show distinct points of occlusion and assist in the diagnosis of pulmonary embolism.

PULMONARY INFARCTION. The roentgenologic signs of pulmonary infarction depend upon the pathologic anatomy of the lesion at the time the examination is made. Shortly after the embolic episode, changes begin to take place in the affected segment of the lung. Blood extravasates into the alveolar spaces, producing a shadow of relatively airless lung. Usually several hours or a day elapses before the changes are sufficiently marked to be made out roentgenographically (Fig. 3, *a* and *b*; Fig. 4, *a*). The involved segment of lung always extends to a pleural surface (Fig. 6, *b*; Fig. 8), either peripherally or at an interlobar fissure. It may be necessary to rotate the patient into some degree of obliquity to demonstrate this fact, but it can always be done if care is taken. The involved segment of lung has been described as having the shape of a truncated cone; but this is an ideal oversimplification, for of course the shape of the segment varies. Usually the broadest diameter is at a pleural surface (Fig. 8).

Because the pleura is involved by the infarct, pleural fluid may accumulate (Fig. 6, *a* and *b*). If the amount is large, the evidence can be seen easily on any type of roentgenogram. If the amount is small, however, an examination in the lateral decubitus position may be necessary to demonstrate it.

With involvement of a pleural surface there may be sufficient pain to

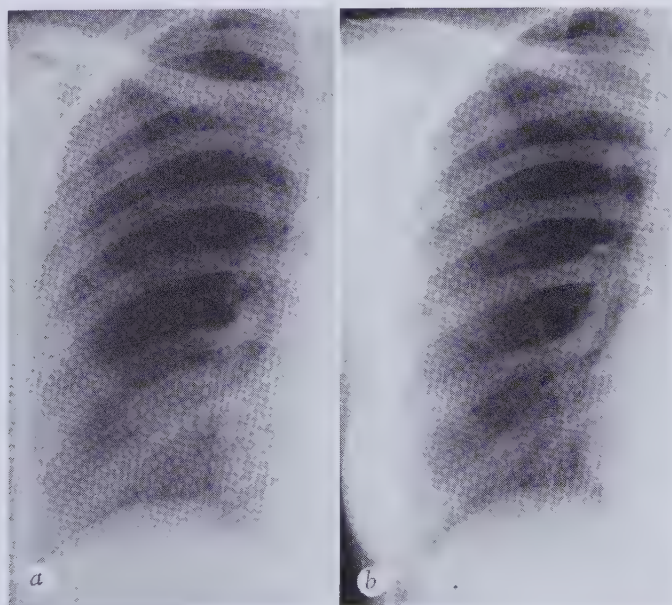


Figure 5 (same case as Fig. 4). *a*, One week later. Infarct is beginning to heal. *b*, Three months after embolic episode. Lung is normal, healed by resolution.

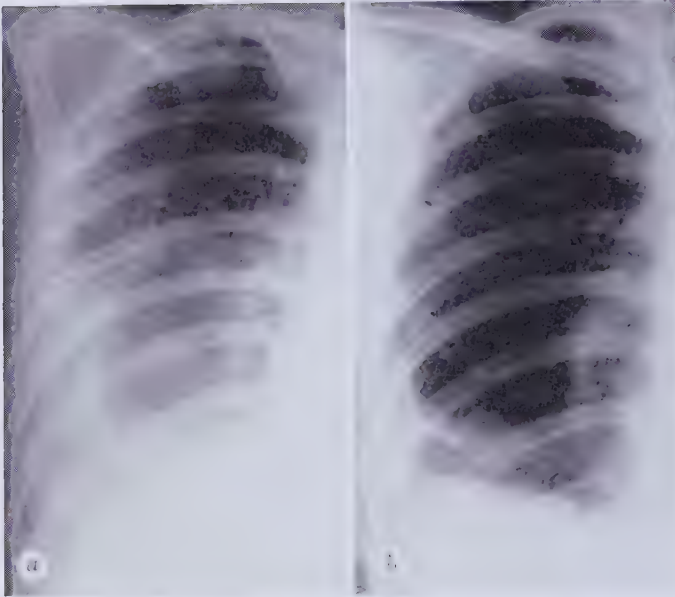


Figure 6. Course of pulmonary infarction following orchitis associated with mumps. Two weeks after orchitis, series of several episodes of right pleuritic pain had begun.

a, Two weeks after onset of pleuritic pain. Large amount of fluid in pleural space obscures lower portion of lung.

b, Three days later, after thoracentesis. Infarct in right lower lobe, extending to pleural surface.

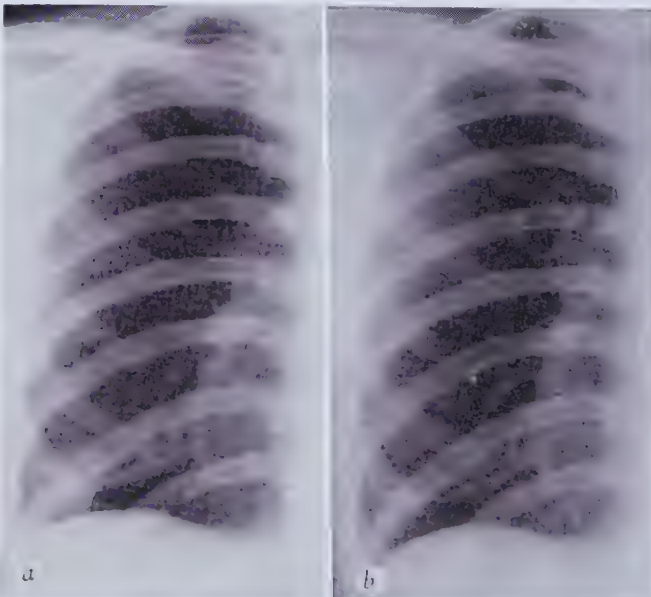


Figure 7 (same case as Fig. 6). *a*, Three weeks after Figure 6, *b*, Pleural fluid has disappeared, lower lobe has expanded into costophrenic angle, and infarct shows signs of healing.

b, Two months later. Only residual sign is small stellate fibrous scar.

cause limitation of respiratory excursion and elevation of the corresponding part of the diaphragm (Fig. 3, *b*). Since diaphragmatic elevation may accompany laparotomy also, not too much reliance should be placed on this feature after such a procedure.

Infarcts are often multiple (Figs. 1 and 2). The simultaneous or, for that matter, progressive appearance of shadows in one or both lungs is as much indicative of pulmonary infarction as of bronchopneumonia.

Pulmonary infarcts may heal by resolution (Fig. 2, *b* and 5, *b*) or by fibrosis (Figs. 7, *b* and 9, *b*), or they may break down to form cavities. The process of healing takes several days to several weeks, and is gradual. Examples are shown in all cases illustrated.

Roentgenologically, pulmonary infarcts are most often confused with pneumonitis and with postoperative atelectasis. A thorough knowledge of the clinical course and physical state of the patient is essential. Usually postoperative atelectasis appears in the first day or two after the surgical procedure. On the other hand, episodes of pulmonary embolism leading to infarction are more common from the sixth to the eighteenth postoperative day, although they may occur at any time.

By the time enough symptoms have developed from pneumonitis or atelectasis to require roentgenologic examination, signs of disease almost always are discernible on the roentgenogram. In pulmonary embolism, however, the reverse is more often true: the lungs may be clear roentgenologically for several hours or a day or more after the symptoms are first noted. Shadows develop later, and examinations should be repeated daily in any case in which an embolic episode has been suspected.

Studies of Blood and Pleural Fluid

Leukocytosis and increase of the rate of erythrocyte sedimentation are the only hematologic abnormalities noted consistently with pulmonary embolism. Occasionally the serum concentration of bilirubin is increased.

Serum glutamic-oxalacetic transaminase (SGOT) remains normal—a feature helpful in distinguishing pulmonary embolism from myocardial infarction. Wacker and associates have described a triad for the diagnosis of pulmonary embolism and infarction: rising serial measurements of serum lactic dehydrogenase during the first four days, elevated serum bilirubin, and normal SGOT. This combination strongly favors the diagnosis of pulmonary embolism and infarction and helps to distinguish them from myocardial infarction, according to these authors.

Pleural fluid, ordinarily bloody and having the characteristics of an exudate, is a usual development with pulmonary infarction. On the other hand, pleural fluid resulting from congestive failure is likely to be clear and have the characteristics of a transudate.

Electrocardiography

Pulmonary infarction produces no electrocardiographic change. Al-

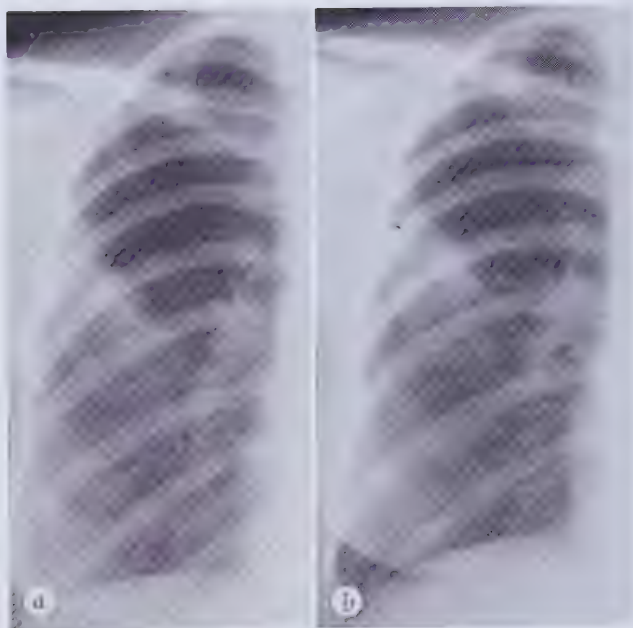


Figure 8. Course of infarction following surgery. Twelve days after cholecystectomy, thoracic pain and hemoptysis were noted.

a, Three days after onset of symptoms. Infarct at level of third anterior interspace, extending to pleural surface.

b, One week later.

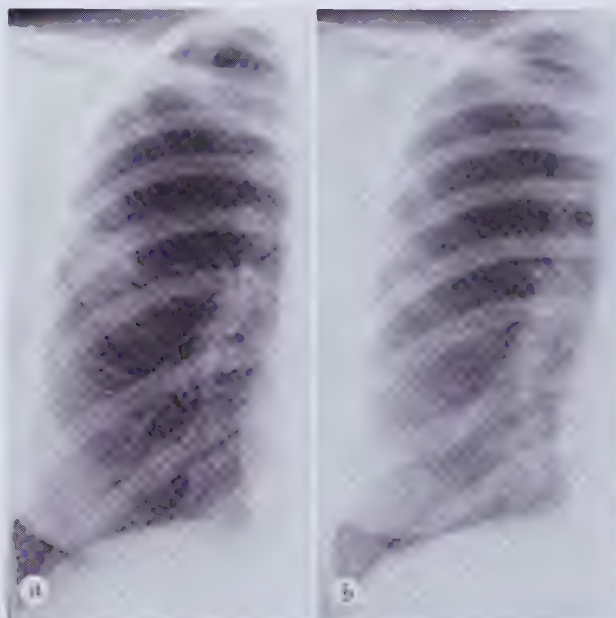


Figure 9 (same case as Fig. 8). *a*, Three weeks after onset of symptoms, 12 days after Figure 8. *b*, Healing has begun and infarct is contracting.

b, Five months after Figure 8. *b*, Healing is complete, only small linear fibrous scar remaining.

though some electrocardiographic abnormalities may be found in two-thirds of the instances of embolism, those cases having characteristic changes of definite help in diagnosis are exceptions, amounting to perhaps 5 to 10 per cent. Acute right ventricular hypertension produces several electrocardiographic abnormalities. Limb leads show sinus tachycardia, a constant S wave in lead I, a frequent Q wave in lead III, inversion of T₃, flattening or slight inversion of T₂, and rather low voltage. Occasionally P₂ is tall and sharp. In chest leads the T wave is inverted frequently in V-1 to V-3, sometimes in V-4, and occasionally in V-5; and the RS pattern is brought around as far as V-5 or V-6. Transient right bundle-branch block occurs in about 15 per cent of cases. The electrocardiographic changes can be expected to return to normal within days or weeks, and their evolution and regression are important in the diagnosis. Comparison with previous electrocardiograms may be of great value.

DIFFERENTIAL DIAGNOSIS

Few other disorders can be so tragic or deceive the experienced physician so often as pulmonary embolism. It must be differentiated from myocardial infarction, pneumonia, atelectasis, pleurisy from whatever cause, lung abscess, chronic pulmonary infection, cancer of the lung and pleura, subphrenic abscess, acute surgical abdomen, syncope, hemorrhage with shock, cerebrovascular accident, convulsive disorder, liver disease with icterus, dissecting aneurysm of the aorta, and other conditions.

Associated thrombophlebitis or a history of previous thrombophlebitis or pulmonary embolism lends strong support for the diagnosis of pulmonary embolism.

CAUSE OF DEATH, MORTALITY, AND PROGNOSIS

If death follows embolism, circulatory collapse from right ventricular strain and failure is ordinarily the immediate cause. The terminal results of massive embolism are usually ventricular fibrillation and acute cardiac arrest. Asphyxia is sometimes a secondary cause of death but is rarely the primary cause. Coronary insufficiency due to lowered blood pressure is believed by some to be a major contributory cause of death.

It is difficult to determine the mortality among all cases of pulmonary embolism because of the large number of mild cases that go unrecognized. Among those recognized the mortality is perhaps between 10 and 30 per cent without anticoagulant therapy, and the prognosis is markedly improved when effective anticoagulant therapy can be administered.

In a series reported by Barker and Priestley, 30 per cent of the patients who survived an attack of pulmonary embolism or infarction had

subsequent episodes of embolism (fatal in 19 per cent). Of those patients who had had clinical thrombophlebitis without embolism, 11 per cent had subsequent thrombophlebitis and 16 per cent had subsequent pulmonary embolism (fatal in 6 per cent). It is clear that patients with a history of previous thrombophlebitis or pulmonary embolism are in a hazardous situation.

TREATMENT OF THROMBO-EMBOLISM

Prevention

Prevention of embolism is directed toward the prevention of thrombophlebitis. One should elevate the legs, avoid pressure on the leg veins, refrain from using leg veins for intravenous medication and fluids, encourage early ambulation or at least early leg motion (not just early sitting), apply elastic bandages to the legs, and—in selected cases—anticoagulant therapy. These measures are distinctly helpful but unfortunately not completely successful. In the postoperative period, prophylactic anticoagulant therapy is indicated for those who have had thrombophlebitis or pulmonary embolism and for older patients who have heart disease or leg trauma or who are obese. When the diagnosis of pulmonary embolism or thrombophlebitis is made, or even strongly suspected, active anticoagulant therapy should be started at once.

Ligation of veins is not done so often as formerly, and is now used only if pulmonary embolism recurs despite adequate anticoagulant therapy or if anticoagulants are contraindicated, as for potential bleeders. Ligation has been largely abandoned because a more effective job can be done with anticoagulant therapy. If ligation is to be effective, the inferior vena cava should be ligated; and the venous insufficiency therefrom can be very distressing. To avoid this disturbance, methods of filtering the blood in the inferior vena cava without obstructing its flow have been devised, such as the plication method of Spencer and co-workers and the vena caval filter method of DeWeese and Hunter. If these or similar methods should prove worthwhile, more frequent use can be anticipated.

Active Therapy

As soon as the diagnosis of thrombophlebitis or pulmonary embolism is made, or even strongly suspected, anticoagulant therapy should begin; and it should be continued until the patient is symptom-free and fully ambulatory. This is usually a period of ten days to three weeks. Should there be a recurrence, long-term anticoagulant therapy is indicated. Hemoptysis from pulmonary embolism does not contraindicate the use of anticoagulants.

When the decision for anticoagulant therapy is made, heparin, 50 mg., is given every four hours at the onset. Begun at the same time is administration of one of the coumarin compounds (Dicumarol, 200 to 300 mg., or warfarin sodium, 35 to 40 mg.). When the prothrombin time reaches the desired therapeutic level, usually after 24 to 48 hours, heparin therapy is stopped but coumarin therapy is continued with carefully controlled dosage. Adequate anticoagulant therapy will save a large majority of those patients who otherwise would die from pulmonary embolism.

Treatment of Cor Pulmonale

During the acute phase of cor pulmonale, therapy should be considered urgent. For the relief of pain and apprehension, morphine or meperidine (Demerol) is effective and urgently needed. Oxygen relieves hypoxia and may be given by mask or oxygen tent. Shock may be treated by intravenous administration of medicaments such as phenylephrine (Neo-Synephrine), 50 to 100 mg., in 5 per cent dextrose in water, or Levarterenol bitartrate (Levophed), 4 ml. of 0.2 per cent solution, diluted to 1000 ml. with 5 per cent dextrose in water. Aminophylline, 250 to 500 mg., in 500 ml. of 5 per cent dextrose in water helps relieve dyspnea. Rapid digitalization is indicated if there is heart failure.

Intravenous administration of papaverine with or without atropine was highly recommended in the past but is now considered of unproved value.

Pulmonary embolectomy is receiving more attention currently, and a number of successful operations have been reported. This procedure should be considered only for patients who have massive embolism likely to cause death unless relieved. It should of course be performed only in centers equipped for thoracic surgery including cardiopulmonary bypass procedures.

Fibrinolysin therapy has been tried and has failed to prove effective against either thrombophlebitis or pulmonary embolism. It has largely been abandoned.

A general evaluation of the worth of these various therapeutic efforts is difficult because many patients die before any therapy can be given while others may survive without therapy of any kind.

SUMMARY AND CONCLUSIONS

In summary it may be said that pulmonary embolism is one of the most frequent and most serious lung disorders. Accuracy of diagnosis is low. We must suspect it in many patients, particularly those beyond the age of 40, those having had surgery, those bedridden from whatever cause, those with chronic diseases such as heart disease and malignant conditions, and particularly those with a history of previous thrombophlebitis or

pulmonary embolism. Roentgenography can help in diagnosing embolism and infarction. Because of frequent inability to make a definite diagnosis, one must sometimes recommend that a patient with a pulmonary complication be treated both with antibiotics for possible pneumonitis or subphrenic abscess and with anticoagulant therapy for suspected embolism. The risk of properly controlled anticoagulant therapy is small and the benefit derived in the treatment of embolism great. We should not hesitate to treat a patient when the diagnosis of pulmonary embolism is merely suspected.

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The Current Status of Idiopathic Pulmonary Fibrosis (Hamman-Rich Syndrome)

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In 1935 and again in 1944 Hamman and Rich^{17, 18} described in detail four unusual cases of idiopathic pulmonary fibrosis with an acute, fatal course and with distinctive histopathologic changes in the lungs at necropsy. Since those original descriptions, interest and information about this usually lethal condition have grown. It has been reported in infants,^{20, 23} in the elderly,⁵ in siblings,^{34, 37} and in identical twins.²⁸ All of the early cases were diagnosed post-mortem, and it was not until 1953 that the first case diagnosed during life was reported.³³

By January, 1963, more than 130 cases of idiopathic interstitial pulmonary fibrosis had been recorded in the literature.^{4, 19, 34} In 1957 Rubin and Lubliner had reviewed 39 cases previously described by others and added 15 of their own. Their extensive study revealed that only a minority of cases followed the acute course originally described. It has become increasingly evident that the duration of the disease in many patients may be measured in years rather than in months, and that other deviations from the initial findings of Hamman and Rich may be encountered. The clinical, roentgenologic, and pathophysiologic characteristics of idiopathic pulmonary fibrosis are not unique and may be simulated by many diffuse involvements of the lung, including the pneumoconioses, diffuse malignancy, the collagen diseases, multiple small pulmonary emboli, and granulomatous processes—especially sarcoidosis.

CLINICAL ASPECTS

The disease is slightly more common in males than in females, and the onset of symptoms is usually insidious. It can begin at any age but

occurs most frequently between 30 and 50 years. The youngest patient reported was an infant of 3 months of age,²⁰ and the oldest a woman of 81.⁵ Dyspnea is the most prominent symptom. At first it occurs only on exertion, but ultimately it is present at rest and is unaffected by position. Cough is also troublesome. It is persistent and may require narcotics for relief. Although a sense of constriction in the chest is commonly mentioned, only a few patients have had hemoptysis or chest pain on exertion. An occasional patient may complain of joint pains and fibrositic symptoms without other evidence of rheumatoid disease. At a later stage weight loss, weakness, and fatigability accompany the downhill course. When fever is present, it usually is due to a superimposed infection. The rapid deterioration in the acute phase of the disease is believed to be most often due to an additional pulmonary insult, frequently an infection.

In keeping with the rather nonspecific character of these symptoms, the physical findings also are not diagnostic. At first cyanosis appears with exercise, but later it becomes obvious even at rest. In the same way, an increased respiratory rate is first apparent as dyspnea on exertion; but as the disease advances, progressively less exertion will cause shortness of breath. Clubbing of the fingers and toes is seen also at a later stage. In the chest, dry crackling rales with the character of crackling cellophane may be scattered throughout both lung fields. Later, increased pulmonary-artery pressure is shown by accentuation of the pulmonic second heart sound; and peripheral edema, hepatomegaly, and elevated venous pressure indicate failure of the right side of the heart to keep up with its burden.

The abnormalities seen on the chest roentgenogram are variable and usually not diagnostic. The most frequent findings are signs of a diffuse process with a reticular, finely nodular pattern most prominent in the middle and lower lung fields. The appearance may suggest granulomatous disease, lymphangitic metastasis, diffuse alveolar-cell carcinoma, or alveolar proteinosis. In the more chronic cases, compensatory emphysema may be demonstrated, sometimes with an accompanying pneumothorax. Less commonly there may be only minimal and focal fibrosis, a perihilar pattern mimicking cardiac decompensation, or changes similar to those of bronchopneumonia.

In general the routine laboratory tests give variable results which are not definitive. The leukocyte count and erythrocyte sedimentation are usually increased only when secondary infection is present. In a few cases mild eosinophilia has occurred. Secondary polycythemia frequently follows prolonged arterial oxygen desaturation. Abnormalities of serum protein—reported in some cases—have consisted of a decrease of albumin and increases of alpha and gamma globulins. Less commonly the response to the latex fixation test for rheumatoid factor in the serum has been reactive or weakly reactive without clinical evidence of joint disease to accompany it. When pulmonary arterial hypertension is present, a right-ventricular hypertrophy pattern develops in the electrocardiogram.

The most helpful diagnostic procedures are the objective measurement of pulmonary disability by pulmonary-function tests and lung biopsy for tissue diagnosis. Without the latter, no conclusive diagnosis can be established before death.

Illustrative Cases

The following four cases illustrate some of the varied clinical, roentgenologic, physiologic, and histologic findings in idiopathic pulmonary fibrosis.

CASE 1. A 60-year-old housewife had been well until March, 1962, when she had noted the onset of aching in her knees, wrists, hands, and shoulders. With a brief course of steroids, this had subsided. In April, she had had a brief episode of pleurisy, and in early July she had noticed exertional dyspnea and a persistent dry cough. A scalene-node biopsy specimen had been regarded as "inflammatory." On July 10 her home physician had prescribed methylprednisolone in doses of 8 mg. every six hours.

She was admitted to the Mayo Clinic on July 27, 1962, afebrile, with a pulse rate of 76 beats per minute and respiratory rate of 36 per minute. There were bilateral diffuse, dry rales; and with any exertion she became cyanotic. Findings from examination of joints were normal. The chest roentgenogram revealed a diffuse patchy, nodular process in both lung fields with elevation of the right hemidiaphragm (Fig. 1). The tuberculin skin test (5 TU) was positive. The hemoglobin concentration and leukocyte count were normal. Results of two clot tests for lupus erythematosus were negative. The result of the latex fixation test for rheumatoid factor was reactive. Electrophoresis of serum protein showed albumin as 2.55 gm./100 ml., alpha-1 globulin 0.33, alpha-2 globulin 0.69, beta globulin 0.85, and gamma globulin 1.35. Sputum smears were negative for tubercle bacilli and cultures revealed the usual flora. Subsequently cultures for tubercle bacilli proved negative also. Administration of steroids was continued, and 300 mg. of isoniazid was given daily. The pulmonary-function tests showed marked reduction in vital capacity and total capacity, unresponsive to bronchodilators. The maximum breathing capacity and nitrogen washout index were normal. There was arterial oxygen

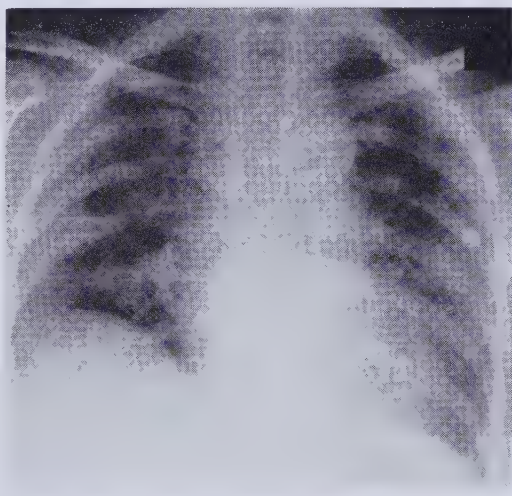


Figure 1 (Case 1). Bilateral diffuse, softly nodular infiltrate in lung fields with elevation of right hemidiaphragm.

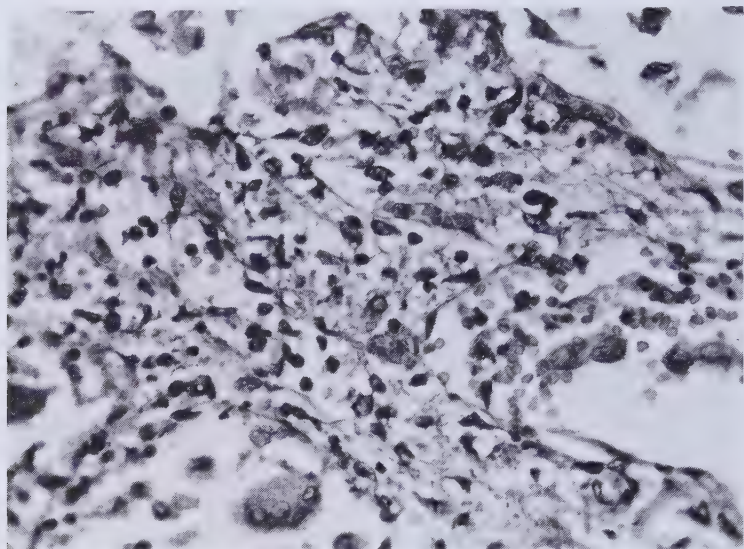


Figure 2 (Case 1). Section of lung shows thickening and disruption of alveolar septa and infiltration of lymphocytes and plasma cells in edematous young fibrous tissue. Also, focal extravasation of erythrocytes, a few macrophages, and a giant cell. (Hematoxylin and eosin; $\times 380$.)

desaturation at rest, accentuated by exercise; and carbon monoxide diffusing capacity was markedly reduced. After two weeks the patient felt better and was able to stroll in the hall; but pulmonary-function tests and chest roentgenography did not show objective improvement.

On August 15, fever appeared and a diagnosis of bronchopneumonia was made. Administration of steroids was increased, and penicillin and streptomycin therapy was begun. She became afebrile; but progressive respiratory insufficiency developed, and she died on August 23, five months after the onset of her illness.

At necropsy, the significant findings were in the lungs, which were heavy and indurated. The right lung weighed 815 gm. and the left 440. The pleural surfaces were smooth. The parenchyma was grayish to yellowish pink and contained scattered dark-red foci of hemorrhage. Opening the major arteries disclosed recent nonadherent pulmonary emboli without pulmonary infarction. The cut surface appeared somewhat consolidated and exuded a serosanguinous fluid. Bronchi contained mucopurulent material.

Microscopy disclosed (Fig. 2) active interstitial pneumonitis in many zones and scattered patchy foci of interstitial fibrosis. The interalveolar septa were thickened by an edematous infiltration of lymphocytes, plasma cells, and a few eosinophils. There was widespread patchy disruption of the alveolar walls with marked capillary hemorrhage. Alveolar cell hyperplasia was moderate, and no hyaline membrane was seen. Many alveoli contained a fibrinous exudate with erythrocytes, scattered macrophages, a few lymphocytes, neutrophils, and an occasional foreign-body giant cell. An increase in reticulin fibers and a few young fibroblasts were noted in the thickened alveolar walls.

CASE 2. An 8-year-old boy had had what his mother believed to be a common cold in December, 1954. This had subsided, but his mother had noticed that he continued to seem tired. In October, 1955, dyspnea and a chronic nonproductive cough had become evident.

The boy was first seen at the Mayo Clinic in April, 1956. He was thin and afebrile, with a pulse rate of 108 and respiratory rate of 24. Mild cyanosis and clubbing of the fingers were noted. The pulmonary second sound was increased and split with inspiration. There were a few dry, crepitant rales in both lung bases.

A diffuse, hazy infiltrate was evident bilaterally in the chest roentgenogram (Fig. 3, *a*). The responses to skin tests for histoplasmosis and coccidiomycosis and to first and second-strength PPD (5 and 250 TU) were negative. The hemoglobin was 11.9 gm. per 100 ml. blood and the leukocytes 10,700 per cu.mm. with a normal differential count. Cultures of gastric washings later proved to be negative for tubercle bacilli and fungi. The electrocardiogram was interpreted as showing a right ventricular strain pattern. Pulmonary-function tests demonstrated a marked reduction in vital capacity and total lung capacity. There was no expiratory slowing on the spirographic tracing, and the nitrogen washout index was normal. The patient was able to perform a simple two-step exercise test for only 1½ minutes, and experienced a slight drop in arterial oxygen saturation.

Treatment with oxytetracycline brought no improvement. On April 20, a right scalene node was biopsied and proved to be inflammatory. A week later the left lung was biopsied. At surgery, the lung was firm and purplish.

Microscopically (Fig. 4), the appearance of the lung was cellular, predominantly because of an infiltration of lymphocytes, plasma cells, and a few eosinophils in the thickened interalveolar septa. There was also moderate proliferation of young

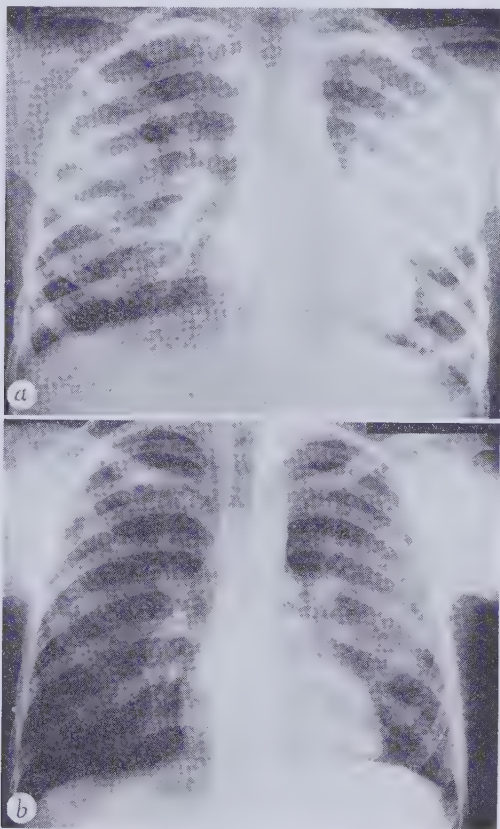


Figure 3 (Case 2). *a*, Bilateral pathologic process in both mid lung fields. *b*, Nearly four years later: perihilar process partly cleared.

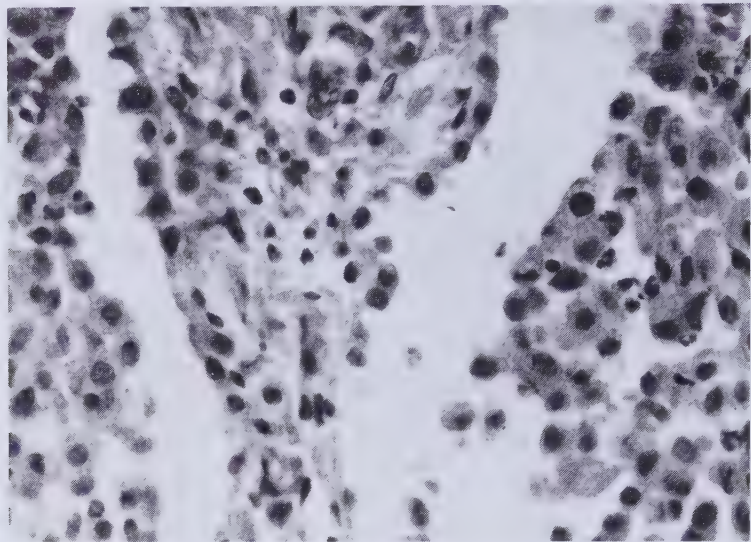


Figure 4 (Case 2). Proliferative interstitial fibrosis and pneumonitis (note cellular appearance), with increase in young septal fibroblasts and hyperplasia and metaplasia of alveolar lining cells, many of which are desquamating into alveoli (hematoxylin and eosin; $\times 560$).

septal and peribronchiolar fibroblasts with associated reticulin fibers but little production of collagen. Alveolar-cell hyperplasia with cuboidal metaplasia was marked. Many alveoli contained desquamated alveolar cells, histiocytes, a few erythrocytes, neutrophils, and eosinophils. Hypertrophy of peribronchiolar and peribronchial smooth muscle was moderate and there was only slight sclerosis of pulmonary arterioles.

The patient was given prednisone, 40 mg. daily; and over the subsequent three months this was gradually tapered to 5 mg. daily, which was maintained until February, 1957. Appetite and tolerance of exercise improved. The dose was gradually reduced further; and in February, 1961, it was discontinued. The last pulmonary-function tests—obtained in November, 1957—still showed small volumes and peripheral arterial oxygen desaturation on exercise. In February, 1961, the chest x-ray showed improvement (Fig. 3, *b*). The patient's mother, in a phone conversation in August, 1962, stated that he had some shortness of breath with hard exertion but he had grown normally and was able to play ball and swim with the other children.

CASE 3. A 54-year-old farmer had had no pulmonary symptoms when first seen at the Mayo Clinic in 1952, and the chest had appeared normal roentgenographically. He had felt well until January, 1960, when he had noticed the onset of exertional dyspnea, irritating dry cough, retrosternal aching on deep inspiration, and some vague aching and stiffness of the hands. He gave no history of smoking or exposure to noxious inhalants. Treatment with rest, aspirin, thimerin, digitalis, and various antibiotics had brought no benefit. In March, 1960, he was admitted to the Mayo Clinic with a pulse rate of 82, a respiratory rate of 24, and bilateral fine inspiratory basilar rales. The venous pressure was estimated to be normal and pitting edema of the ankles was minimal at the time of initial examination. On the day after admission, the body temperature rose to 101° F.

Hemoglobin measured 15.6 gm. per 100 ml. of blood. The leukocyte count,

differential leukocyte count, and erythrocyte sedimentation were normal. Serum-protein electrophoresis revealed mild reduction in albumin, but the other fractions were normal. The sputum was negative for malignant cells and cultures for tuberculosis and fungi were negative on numerous occasions. Chest roentgenograms made elsewhere in January, 1960, showed bilateral basilar infiltrates. Those made on this admission here were interpreted as showing "pulmonary vascular congestion in both bases" (Fig. 5, *a*). Pulmonary-function tests revealed a marked decrease in vital capacity and total capacity and moderate impairment of maximal breathing capacity. Significant arterial oxygen desaturation occurred after only 1½ minutes of exercise.

Treatment for congestive heart failure produced no improvement; and on April 28, biopsy of a scalene node proved it inflammatory. Right lung biopsy then revealed marked infiltration of the alveolar walls by inflammatory cells (Fig. 6, *a* and *b*). There was slight thickening of the alveolar walls, due to the presence of young fibroblasts with increased reticulin and a little collagen (Fig. 6, *c*). The interstitial and elastic fibers were fragmented in some zones. The alveolar lining cells were hyperplastic and cuboidal throughout, and in some areas they desquamated into alveoli. All in all, this had the appearance of interstitial pneumonitis with early interstitial fibrosis.

Administration of prednisone was begun with doses of 10 mg. every six hours,

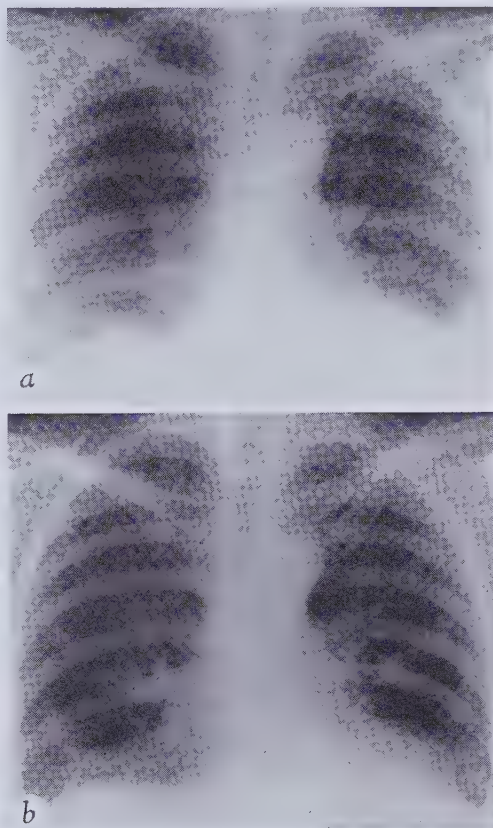


Figure 5 (Case 3). *a*, Involvement of both lung bases by diffuse process, also present but less marked in remainder of lungs. *b*, Nearly three years later: slight improvement in both lungs.

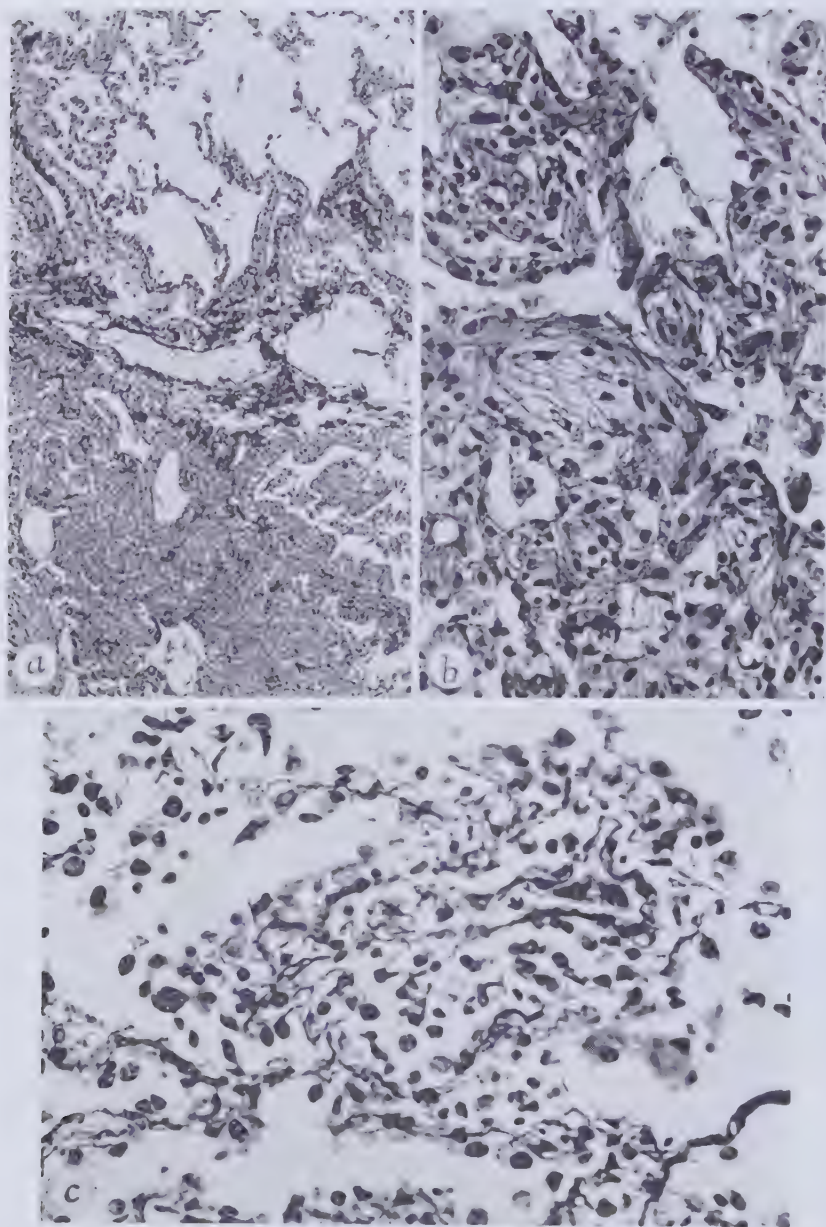


Figure 6 (Case 3). *a*, Irregular distribution of interstitial fibrosis is evident from increased cellular interstitial infiltration at left (hematoxylin and eosin; $\times 60$).

b, Nodular proliferation of young fibrous tissue (Masson body, at center) and interstitial infiltration of mononuclear cells (hematoxylin and eosin; $\times 250$).

c, Abundant reticulin in cellular septal walls (Gomori's reticulum stain; $\times 480$).

then reduced gradually over a period of several months to 5 mg. daily. The patient felt better but the dyspnea did not improve and the roentgenographic signs did not change. Pulmonary-function tests three months after the start of treatment showed improvement in maximal breathing capacity, but the limitation of pulmonary volumes and the decrease of oxygen saturation persisted.

The patient was seen frequently—most recently in February, 1963, at which time he was taking prednisone, 5 mg. twice daily, and feeling much improved. He was able to climb one flight of stairs with some dyspnea but no cough. The roentgenographic appearance of the chest (Fig. 5, *b*) had cleared only slightly since 1960; but the arterial oxygen saturation had improved.

CASE 4. A 50-year-old farmer who came to the Mayo Clinic in July, 1959, had smoked two packages of cigarettes daily for many years but gave no history of other noxious inhalants. He first had noticed the onset of exertional dyspnea in 1957. He had had a chronic cough producing 1 to 2 tablespoonfuls of yellow to white sputum daily. Also, he had had three hemorrhages from a duodenal ulcer. Progression of the dyspnea was his reason for coming to this clinic.

On physical examination, the patient was afebrile and the pulse and respiration were normal. Auscultation revealed bilateral basilar rales. Limitation of chest expansion was noted. The hemoglobin concentration and leukocyte count were normal. Response to the second-strength (250 TU) skin test was positive. A chest x-ray (Fig. 7) showed fine, nodular infiltration of both lower lung fields, greater on the left. Roentgenograms made elsewhere helped to demonstrate progression of this disorder since December, 1957. An electrocardiogram was not remarkable.

Pulmonary-function tests revealed reduction in vital capacity and total capacity with normal maximum breathing capacity, not improved by bronchodilators. There was no arterial desaturation at rest, but with less than two minutes of exercise the saturation dropped to 65 per cent.

An excised scalene node was regarded as inflammatory on histologic examination, but lung biopsy demonstrated advanced interstitial fibrosis (Fig. 8). The interalveolar septa were markedly thickened by sheets and strands of fibrous tissue with mature fibroblasts and collagen. There was an associated increase of reticulin while the elastic tissue was fragmented, clumped, and apparently decreased in quantity. The interstitial mononuclear cells (lymphocytes, plasma cells, and histiocytes) were only slightly increased. The alveolar lining cells demonstrated striking hyperplasia and metaplasia, with areas forming sheets of cuboidal to



Figure 7 (Case 4). Finely nodular process in both lung fields, most obvious in the lower third on each side.

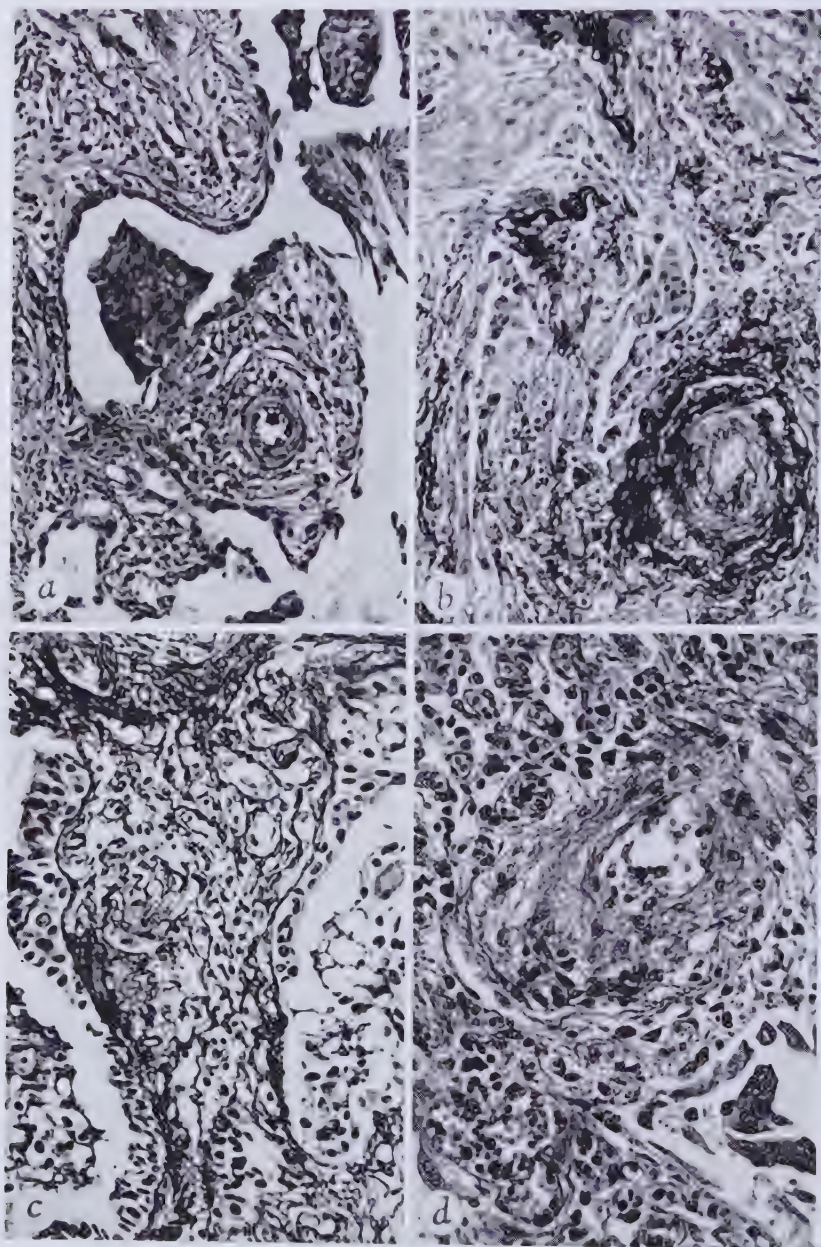


Figure 8 (Case 4). Advanced interstitial fibrosis with collagenization. *a*. Distortion of alveoli by marked septal fibrosis. Note proliferation of alveolar cells. (Hematoxylin and eosin; $\times 175$.)

b. Fragmentation and clumping of elastic fibers in zones of fibrosis (van Gieson's elastic-tissue stain; $\times 225$).

c. Alveolar-cell hyperplasia, metaplasia, and desquamation and marked reticulin production (Gomori's reticulum stain; $\times 245$).

d. Pulmonary vascular sclerosis and focal capillary proliferation in fibrous tissue (hematoxylin and eosin; $\times 300$).

squamous epithelium, at times filling the alveoli. The bronchiolar walls were thickened by a moderate increase in smooth muscle and some hyperplasia of lining cells. Most of the pulmonary arteries and arterioles had changes of moderate to marked vascular sclerosis as evidence of pulmonary hypertension.

Administration of steroids was begun, but the patient died 10 days later of a massive gastric hemorrhage. At necropsy, this was found to have resulted from erosions of gastric mucosa. The duodenal ulcer was healed. Both lungs were rather airless, congested, indurated, and heavy; the right lung weighed 1175 gm. and the left 810 gm. The tracheobronchial tree contained a mucopurulent exudate due to bronchopneumonia. Sections of lung revealed pathologic features like those seen at the biopsy and diffuse involvement by advanced collagenous interstitial fibers, with no demonstrable change from steroid treatment. Inflammatory foci of bronchopneumonia were seen and cultures revealed staphylococci.

PATHOPHYSIOLOGY

The term *alveolocapillary block* indicates that a significant defect in gas diffusion exists at the alveolocapillary membrane.² Diffuse interstitial pulmonary fibrosis is one of many diseases that may cause this impairment of function. The principal physiologic abnormality is a reduction in the diffusing capacity of the lung. Reduced lung volumes, hyperventilation, and absence of obstructive ventilatory disease are other important distinguishing features.

Although the residual volume and total lung capacity are diminished, the airway resistance is not usually increased; and consequently the maximal breathing capacity and the maximal mid-expiratory flow rates are fairly normal also. In severe cases, increase of the physiologic dead space and venous admixture may be encountered. This may be accounted for in part by focal emphysema or poorly perfused areas of lung which continue to be ventilated.

The patients have stiff lungs with reduced compliance, so ventilation is achieved most effectively by a rapid respiratory rate and small tidal volume. This hyperventilation results in an increase of alveolar oxygen concentration sufficient to prevent any marked decrease in resting peripheral arterial oxygen saturation, unless the diffusing capacity has been reduced to half or less of the anticipated normal value. Owing to hyperventilation, carbon-dioxide tensions are low, both in the alveolar air and in the arterial blood. Since carbon dioxide diffuses much more rapidly than oxygen, however, its exchange with the alveolar air is not seriously compromised by reduction in the diffusing capacity.

During exercise, passage of increased cardiac output through a diminished pulmonary vascular bed can result in an increase in the velocity of blood in the capillaries. It has been suggested that this produces a reduction in the contact time during which diffusion may take place, which would have the result of raising the alveolar-arterial oxygen end gradient during exercise and producing peripheral arterial desaturation.²¹ Rossier and

associates have concluded that reduction in the capillary surface area is at least as important as the anatomic alteration in the alveolocapillary membrane. In addition, the increased pulmonary blood flow during exercise may raise the pulmonary-artery pressure because of failure of the reduced pulmonary vascular bed to decrease its resistance in the normal manner. Right ventricular overload develops, leading ultimately to decompensation.

HISTOPATHOLOGY

Hamman and Rich^{17, 18} originally outlined the histopathologic features of the idiopathic pulmonary fibrosis which bears their names as follows: (1) inflammation that includes edema and hemorrhage with few leukocytes, in contrast to the ordinary pneumonias due to bacteria; (2) metaplastic enlargement of alveolar lining cells; (3) necrosis of alveolar and bronchial epithelium; (4) hyaline membranes lining the alveoli; (5) edema and deposits of fibrin in the alveolar wall; (6) extensive and diffuse proliferation of fibrous tissue throughout all lobes, associated with focal organization of intra-alveolar hemorrhage; (7) interstitial eosinophils; and (8) absence of stainable bacteria.

They also pointed out that, because of widespread connective-tissue hyperplasia in the pulmonary interstitial structures, the alveolar walls become thickened with fibroblasts which are replaced later by scar tissue. Hamman and Rich were quick to note that one may see different stages of the disease in the same case, from acute inflammation to complete fibrosis, and that dilatation of the right ventricle and myocardial insufficiency may occur as consequences of pulmonary hypertension.

Dissimilar Courses and Recognition

More recent reports^{3, 19, 34} have described cases with some but not always all of the histopathologic features listed above; and these cases have more often pursued a subacute or chronic course, with the patient dying in a few years, rather than the acute, fulminating clinical course of those described by Hamman and Rich. Similarly, it has become apparent that the diagnosis of idiopathic interstitial pulmonary fibrosis depends on both clinical and pathologic grounds—and of course it depends partly on exclusion of other conditions or agents that may produce interstitial fibrosis. Of their 34 cases in which findings from biopsies were compatible with idiopathic pulmonary fibrosis, Herbert and associates excluded 15 because of other possible causes for the disease.

Lung biopsy is important in this diagnosis.³⁰ Similar clinical and radiographic findings may be seen in a host of diffuse pulmonary diseases such as alveolar-cell carcinoma, sarcoidosis, histoplasmosis, and alveolar proteinosis. When a biopsy specimen shows interstitial pulmonary fibrosis (which usually is associated with some degree of pneumonitis), a proper

tissue examination should include microbiologic culture, histopathologic study, and possibly special studies such as chemical or x-ray diffraction analyses for any pulmonary irritant the patient is known or suspected to have encountered.

In cases currently classified as idiopathic pulmonary fibrosis, the pathology may vary from an active or proliferative process with minimal fibrosis, usually associated with subacute or chronic interstitial pneumonitis, to a collagenous or desmoplastic reaction that may or may not demonstrate pneumonitis. Certainly, as Hamman and Rich noted, a fulminating proliferative phase (like that in our Case 1) may produce a rapid demise or the process may be continuous and produce variable degrees of fibrosis in different portions of the lungs. In some cases, however, (as in Cases 2 and 3) the cellular, more inflammatory-appearing lung tissue may indicate a possibly favorable response to proper medical therapy, whereas that showing older collagenized distorted parenchyma (as in Case 4) is more likely to be beyond therapeutic restoration.

In the *early proliferative reaction*, lung biopsy reveals a cellular appearance. This is due to an infiltration of inflammatory cells (particularly lymphocytes, plasma cells, and scattered eosinophils), which are located within the walls of alveoli and alveolar ducts and in peribronchiolar tissues. The fibroblastic proliferation may be difficult to discern in the early stages, with only a few young fibroblasts noted in the inflammatory reaction. Focal nodular septal collections of young fibroblasts may be seen in some cases, however; and invariably there is an increase in parenchymal reticulin, the precursor of collagen.

Associated with the inflammatory reaction is a marked proliferation and metaplasia of alveolar lining cells, which are cuboidal or low columnar. These may be seen to desquamate into the alveoli and become indistinguishable from macrophages. Occasionally a foreign-body type of giant cell may be encountered in the alveoli or the interalveolar septa.

Little actual collagen and few hyalinized areas are seen in the early phases, and there is little architectural distortion in the lung. Detailed studies of the pulmonary alveolar membrane¹²⁻¹⁶ in chronic induced interstitial pneumonitis and fibrosis among guinea pigs,^{12, 16} in organizing pneumonitis,¹⁵ and in the Hamman-Rich syndrome¹⁴ were made by Gross. He pointed out that in chronic interstitial pneumonitis of the accretive type, as seen in Hamman-Rich syndrome, the proliferative alveolar lining cells produce a supporting reticulin stroma which is integral with the axial alveolar reticulin. And if this stroma retains its reticulin character, the lesion is reversible, with fragmentation and lysis of the stroma; or if the stroma collagenizes, the lesion is not reversible.

In cases of *advanced interstitial fibrosis* with collagenization, the gross lung is heavy and often noncrepitant, and appears granular, nodular, or cirrhotic. On cross section it may appear gray and fibrotic or cystic and honeycombed. There is marked distortion of pulmonary parenchyma; and

the alveolar walls are irregularly thickened at the expense of the air spaces, which are irregular in outline, angulated, and markedly reduced in size. Fibrous developments obliterate many alveolar capillaries and scattered small arteries. Veins may be dilated and show foci of old or recent hemorrhage, and there is bronchiolar fibrous stenosis with foci of compensatory emphysema or larger cyst formation (honeycombing) due to septal breakdown and fusion of air spaces. Focal bronchial ectasia and retention of mucus may also occur.

Concomitantly with pulmonary hypertension, pulmonary vascular sclerosis with intimal fibrosis and medial hypertrophy frequently affects small and medium-sized pulmonary arteries and arterioles. (This is commonly reflected also in the hypertrophy and dilatation of the right ventricle of the heart at necropsy.)

The pulmonary fibrous proliferation becomes well developed and dense, and some collagen fibers may be hyalinized. Elastic fibers are often decreased in quantity and fragmented, while bronchiolar smooth muscle appears hypertrophic. The interstitial inflammatory infiltration is slight to moderate in degree, and is composed predominantly of lymphocytes, plasma cells, and some histiocytes. Focal aggregations of lymphocytes may be seen. However, a superimposed bronchopneumonia with suppuration is not an unusual finding at necropsy.

In the *later stages* of the disease, the alveolar epithelial metaplasia may be even more striking. The cells involved may be sharply cuboidal or even tall columnar; and they may simulate neoplastic gland formation in shrunken alveoli. Often alveoli are partially filled by proliferation and desquamation of these cells. Intra-alveolar macrophages may contain small amounts of lipid or hemosiderin, and some demonstrate foreign-body formation.

In the *final stages*, the lung is dense and contracted by fibrosis and has patchy emphysema due to marked architectural disruption. In consequence, much of the respiratory surface is lost and there is marked interference with exchange of gases across the remaining fibrotic alveolar walls. The effective vascular bed is reduced.

Hyperplasia of septal capillaries has been reported by Golden and Bronk which, according to Baglio and associates, resembles the proliferation of blood vessels seen in granulation tissue and occurs in areas of fibrosis. The pleural surfaces may be uninvolved or may show old fibrosis or recent fibrinous adhesions. In the proliferative stage the process may be patchy, sparing some parenchyma, though scattered widely through the lung; but later, in the collagenous stage, the involvement frequently is diffuse and confluent.

Diseases to be Differentiated

Interstitial fibrosis which pathologically is rather similar may be encountered in a variety of diseases, such as radiation fibrosis,³⁶ rheumatoid

disease,^{6, 33} scleroderma, and fibrosis associated with prolonged antihypertensive therapy with hydralazine or hexamethonium.^{7, 25} In addition, pneumoconiosis (such as berylliosis⁸ and asbestosis) long-standing chronic passive congestion of the lungs due to mitral and aortic stenosis,¹¹ congenital dysplasia of the lungs,²² histiocytosis X, sarcoidosis, lupus erythematosus, polyarteritis nodosa, and obstruction of pulmonary veins¹ sometimes mimic this disease pathologically.

ETIOLOGY

In the study of possible causes of idiopathic pulmonary fibrosis, prime consideration has been given to tissue hypersensitivity or allergy. This choice is supported by the finding of similar fibrosis in certain known collagen disorders, such as rheumatoid arthritis,³³ the response of some patients to steroids, the tissue eosinophilia, and the production of similar lesions in rats given rabbit anti-rat-lung serum intratracheally.³¹

However, alveolar-cell hyperplasia and metaplasia and an occasional hyaline membrane have suggested the possibility of inhaled noxious substances or of viral disease such as primary atypical pneumonia, influenza, and pleuropneumonia infections. Since the residue of certain infections may cause interstitial scarring, and since interstitial pneumonitis is a major component of the early lesion, such possibilities are difficult to dismiss. McCordock and Muckenfuss have favored a viral theory supported by their experiments. Herbert and associates reported negative results from viral studies in two of their series. Whether lymphedema⁴ or obstruction of the pulmonary veins^{19, 23} are factors in the pathogenesis of this disease remains obscure. Gross has suggested that the Hamman-Rich syndrome is basically a diffuse, chronic interstitial pneumonitis of unknown cause or causes. Pokorny and Hellwig suggested that repeated attacks of interstitial pneumonitis with a deficiency of fibrinolytic enzymes to remove the inflammatory exudate may produce diffuse fibrosis.

Baglio and associates pointed out that the literature recorded 10 instances in which twin sisters, mother and daughters, sisters, and brothers were involved. The familial incidence is approximately 7 per cent, which is higher than one would expect for a relatively rare disease.

TREATMENT AND PROGNOSIS

The prognosis is poor in the majority of cases, and the course usually is one of progressive pulmonary insufficiency. The duration of the illness is extremely variable, however, and has ranged from 31 days¹⁸ to 15 years¹⁹ in reported cases. Most patients survive two to four years from the onset of their disease. Complete and permanent arrest is exceptional. The

immediate cause of death is respiratory insufficiency often aggravated by a pulmonary infection or by right-heart failure.

Its relentless course and the absence of a specific drug make the problem of treatment for idiopathic pulmonary fibrosis discouraging. Adrenal corticosteroids are the best currently available therapy, but after more than 10 years of experience their efficacy is still under discussion.^{3, 6, 9, 26, 29} The initial dose is usually high: most commonly 40 mg. of prednisone or the equivalent of another steroid has been used. This level is maintained for two to six weeks, depending on the patient's response, and is tapered gradually to the lowest level compatible with sustained clinical improvement and the avoidance of undesirable side effects. In most cases symptomatic relief but little measurable improvement in pulmonary function has followed this method of treatment. Herbert and associates found no improvement in roentgenographic manifestations, capacity, or pulmonary-artery resistance after the use of these drugs. Once started, administration of steroids may have to be continued indefinitely; and the decision to stop becomes difficult and dangerous. Death has been reported to follow cessation of such treatment.^{3, 27} In the four cases described in this paper, steroid treatment improved pulmonary ventilation but did not measurably affect alveolar-capillary diffusion.

It cannot be stressed too strongly that the prevention and prompt treatment of respiratory infections are important and may be lifesaving. Avoidance of overcoughing, cigarette and other smoke, dusty atmosphere, and the like is helpful in reducing the irritation to which the tracheobronchial tree is usually subjected. Copious use of fluids, expectorants, and heated aerosols may be beneficial and aid in the raising of secretions, should this prove to be a troublesome aspect of the problem.

SUMMARY

Idiopathic interstitial pulmonary fibrosis is a clinicopathologic entity of unknown etiology characterized by progressive, usually diffuse, interstitial pulmonary fibrosis associated with variable degrees of interstitial pneumonitis. Clinically there is progressive dyspnea with cyanosis, often clubbing of the extremities, and widespread dry crepitant rales in the lungs. Roentgenologically the most common findings are those of a diffuse, often nodular, infiltrative process in both lung fields. Reduction of lung volumes and impairment of diffusing capacity are the characteristic derangements of pulmonary function. The only method for establishing the diagnosis definitively is lung biopsy. Although no specific treatment is known which will result in a certain cure of the disease, adrenal cortical steroids offer some hope of amelioration.

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Lung Purpura and Pulmonary Hemosiderosis

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Pulmonary changes may occur in many systemic diseases, and the chest roentgenogram is invaluable for early discovery of them. Such changes can accompany many of the collagen diseases—which in our present state of knowledge can include lung purpura and primary pulmonary hemosiderosis³—and may constitute the first and most striking features found.

Lung purpura is a most interesting and important clinical syndrome. It usually occurs in men between the ages of 20 and 30 years. Ordinarily the first symptom is hemoptysis due to diffuse bilateral hemorrhage into the parenchyma of the lung. A roentgenogram of the chest made at this time shows a very characteristic pattern—a butterfly-wing type of infiltrate radiating peripherally from each hilar region. The apices and costophrenic portions of the lung usually are spared (Fig. 1, *a*). The increase of density in the involved portions of lung is due to a large amount of blood released into the alveolar spaces (Fig. 1, *b*). The chest roentgenographic findings may vary and at times may clear up completely without treatment, but they soon reappear with another episode of hemoptysis.

In the past such findings have been mislabeled “uremic lung.” Actually, hemorrhage into the alveolar spaces may occur in uremia and may produce evidence of this kind; but patients who are not uremic may afford such evidence too. It may appear early in a hypersensitive state such as pulmonary purpura. Rusby and Wilson think that lung purpura is very similar to Schönlein-Henoch purpura except for affecting the lungs rather than the skin, joints, and alimentary tract. Glomerulonephritis is commonly associated and is the most frequent cause of death among cases of both kinds.

Probably the method by which a given antigen enters the body determines the various clinical courses that may develop. We strongly suspect that lung purpura represents a hypersensitivity to certain toxic sprays used to control weeds and insects on the farm. It is possible that exposure to other toxic substances might precipitate this somewhat rare

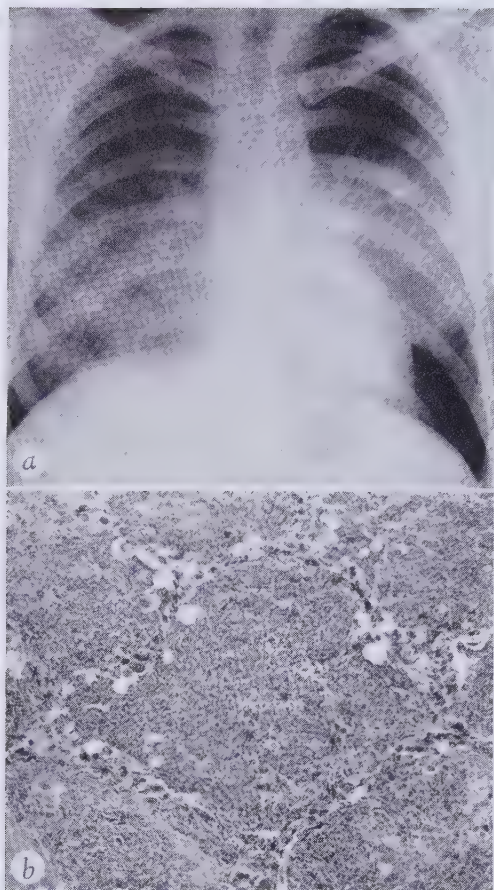


Figure 1. Pulmonary purpura. *a*, Roentgenographic appearance. *b*, Microscopic appearance (hematoxylin and eosin; $\times 235$).

but highly important disease. After repeated exposures, a previously well young farmer might become sensitized to these toxic substances rather suddenly. Then, when the antigens are inhaled again and contact an extensive area of the alveolar surface, the reaction of these tissues can be quite overwhelming. Hemorrhage into the alveolar spaces, swelling, and cellular infiltration of alveolar septa may occur. Vascular changes typical of polyarteritis nodosa are common.

When the patient first consults his physician the urine may be normal, but very soon microhematuria appears. This is the first clinical finding of glomerulonephritis. It is possible that the same antigen which creates such a violent reaction in the lung causes the glomerulonephritis after being absorbed into the bloodstream and carried to the kidney.

¶ Hemoptysis has been mentioned as the first symptom. Cough and weakness also may occur. The body temperature may rise to 102° F. The hemoglobin concentration may drop to 6 gm./100 ml. of blood in a rather short period.

This condition has been misdiagnosed and called pneumonia, farmer's lung, fungous disease, tuberculosis, and pulmonary edema. To save the patient, it is of extreme importance that the disorder be recognized early and treatment with steroids initiated. My colleagues and I have given drugs such as prednisone in doses sufficient to control the hemoptysis and the microhematuria.

Parkin and associates in 1955 reported the first experience with this disease at the Mayo Clinic under the title, "Hemorrhagic and Interstitial Pneumonitis." They described seven cases, all of them fatal. Four of the patients showed evidence of polyarteritis nodosa.

There is definite evidence that primary pulmonary hemosiderosis may be a variant of pulmonary purpura. Most of the patients who have primary pulmonary hemosiderosis are children, and most of those who have lung purpura are young men. Primary pulmonary hemosiderosis may last for years, rather than for months; and glomerulonephritis is not so frequent nor so prominent a finding.

We have observed a most instructive case at our institution. The patient was a 12-year-old boy who had experienced recurrent hemoptysis over 10½ years. Roentgenography of the chest revealed a fine diffuse

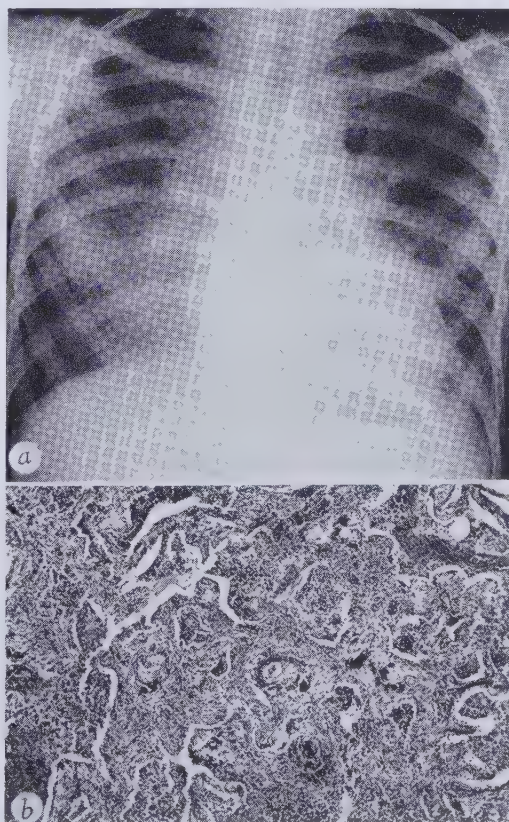


Figure 2. Pulmonary hemosiderosis. *a*, Roentgenographic appearance. *b*, Section of lung showing fibrosis, hemosiderosis, and hemorrhage (hematoxylin and eosin; $\times 55$).

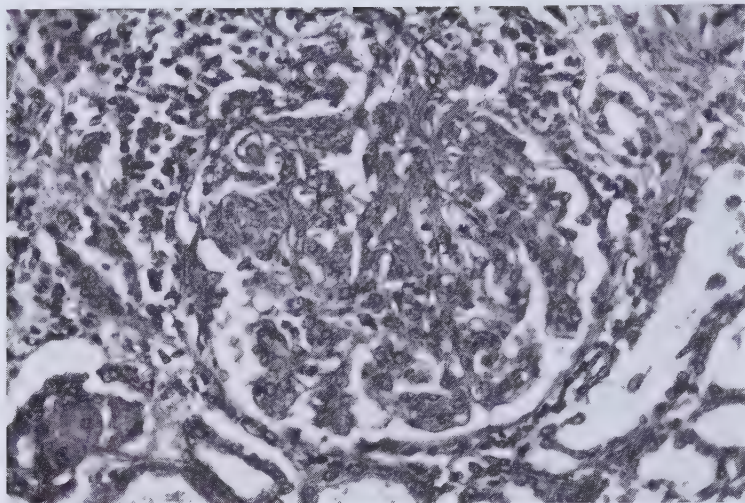


Figure 3 (same case as Fig. 2). Associated acute nephritis (hematoxylin and eosin; $\times 230$).

infiltrate throughout both lung fields, which finally was thought by Dr. André J. Bruwer, then a member of our Section of Roentgenology, to be due to primary pulmonary hemosiderosis (Fig. 2, *a*). After this patient's death the diagnosis was substantiated. There was evidence of periarteritis nodosa in the lungs (Fig. 2, *b*) and kidneys (Fig. 3). This association of findings strongly suggests that the two conditions are different manifestations of the same disease process. It may be that the age at which this hypersensitivity reaction develops determines the manner and the extent of injury to the various tissues of the body.

SUMMARY

An important clinical syndrome which has been called "lung purpura," "necrotizing alveolitis," and "hemorrhagic and interstitial pneumonitis with nephritis" is described. Primary pulmonary hemosiderosis is probably a variant of this condition. Early diagnosis is important, so that proper therapy with steroids may be instituted.

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Lung Involvement in the Connective-Tissue Disorders

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The morbid anatomists of the last part of the nineteenth century were not convinced that the intercellular substance had any significant function other than to act as a support for the cells. It was for this reason that recognition of the activity of the connective tissue in disease was so long delayed. As the understanding of the dynamic functions of the connective tissue grew, so did realization that this might be the site of primary disease. It was left to Klemperer and his colleagues to propose such a concept; but they pointed out that although the connective tissue throughout the body is affected in systemic lupus erythematosus and scleroderma as well as in rheumatic fever, involvement of the connective-tissue system by these diseases did not necessarily mean that they were etiologically related to each other. Although the term "collagen disease" has been applied to the members of this group, it has come to be recognized that since the involvement is not restricted to collagen, "connective-tissue disease" is a more accurate term.

The connective tissue is an extracellular structure and is composed of a physiologically active ground substance containing fibrils of collagen, elastin, or reticulin. Alteration in the chemical composition and physical constitution of the ground substance is thought to be responsible for many of the connective-tissue diseases, which have in common mucinous edema, fibrinoid degeneration, and vascular lesions as their principal pathologic features along with an increase in fibroblasts, mast cells, and lymphocytes.

Within the last decade it has come to be accepted, not only that an animal may produce antibodies against its own specific antigens, but further that such auto-immune responses may be of great importance in producing disease. With the connective-tissue disorders, immunologic abnormalities are found frequently and are largely confined to gamma-globulin antibodies found in the blood and tissues. Certain families have an unusually high incidence of connective-tissue disease because of an inherited alteration of immune mechanisms or some other variation in the connective tissues themselves.¹⁸

The presence of serum factors capable of reacting with endogenous antigens is not sufficient proof that these are in fact pathogenic, and it remains possible that they may be the result rather than the cause of the tissue damage present. Considerable overlap has been shown to exist between the various antibodies described in the different connective-tissue diseases.²⁰ The recognition of these circulating antibodies has been of importance in calling attention to the presence of altered immune mechanisms and in providing the basis for valuable laboratory tests. It should be emphasized that some of the most damaging of immunologic reactions are induced not by circulating serum antibodies but by specifically sensitized cells. Involvement of the lung may occur in any of the connective-tissue diseases; and while there is frequently nothing specific about their clinical or roentgenographic features, they are of great interest to the clinician both as an aid in establishing the diagnosis and as a challenge to determine the mechanisms which produce them.

SYSTEMIC LUPUS ERYTHEMATOSUS

A disease predominantly affecting young females in the reproductive age, systemic lupus erythematosus produces lesions in the connective tissue of many organs and structures throughout the body, particularly the skin and joints. Its course varies from fulminating and rapidly fatal to relatively mild and chronic. Because the distribution tends to be haphazard, unusual assortments of atypical lesions may be present for many years without the diagnosis being established. While genetic factors appear to play some part in the pathogenesis of this disease, their influence is not yet clearly determined.²³ Familial occurrence of systemic lupus erythematosus has been reported; and in some instances of it, elevated concentrations of gamma globulin have been found in apparently healthy members.²⁶ The etiology of systemic lupus erythematosus, like that of the other connective-tissue disorders, remains unknown.

The classic lupus-erythematosus (L.E.) cell formation is an *in vitro* phenomenon induced by a factor in the serum of patients. This factor is a gamma globulin containing auto-antibodies against portions of the cell nucleus. It displaces histones from their normal combination with nuclear desoxyribonucleic acid, which then becomes associated with the L.E. factor and is rendered susceptible to phagocytosis by actively phagocytic cells, usually polymorphonuclear neutrophils. In addition, a number of anti-nuclear and anti-cytoplasmic factors—including antibodies directed against mitochondria² and microsomes¹²—have been described. Circulating anticoagulants and antibodies against leukocytes and platelets have been found in some patients with systemic lupus.²¹ Because of the wide range of immunologic disturbances associated with this disease, it is a most important entity in the further understanding of auto-immunity and of the

connective-tissue disorders. While it appears related to rheumatoid arthritis, the two are best regarded as separate diseases.⁷ Although it has not proved possible yet to reproduce systemic lupus erythematosus experimentally, a syndrome which closely resembles it may complicate the treatment of hypertension following the prolonged use of hydralazine.²⁵

The hematoxylin body is the *in vivo* equivalent of the L.E. cell, and in the classic form of this disease it is found in the tissues of many organs. The connective tissue of the vascular system, the dermis, and the serous and synovial membranes are predominantly affected; and lymphadenopathy, endocardial lesions, onion-skin lesions in the spleen, and wire-loop lesions in the glomeruli may all be found. In the lungs the pathologist may find bronchopneumonia, hemorrhage, interstitial pneumonia, and consequent regional atelectasis. Purnell and associates described a basophilic mucinous edema in the alveolar walls and in the peribronchial and perivascular tissues. These abnormalities are not specific for systemic lupus erythematosus, however; they also have been found in the lungs of patients with other connective-tissue disorders.

It has been recognized for many years that both pleural and pulmonary involvement is common with systemic lupus erythematosus. In keeping with the nonspecific nature of the pathology found in the lungs, the respiratory symptoms are protean and reveal little or nothing of the underlying nature of the disease. Cough is the most frequent complaint and is usually accompanied by mucoid sputum.¹ Hemoptysis is rare. Dyspnea and pleuritic pain, which may be bilateral, are other prominent symptoms. Effusions sometimes are massive; most frequently the results of examination of aspirated fluid are nonspecific, although L.E. cells have been found occasionally.³⁷ Pleural adhesions with obliteration of the pleural space and splinting of the lung and diaphragm are frequent sequels of lupous pleurisy. Pulmonary manifestations may appear early in its course and provide one of the first indications that a significant disease process is present.

The roentgenographic patterns encountered are varied, and extensive pulmonary changes may be demonstrated in the absence of any respiratory symptoms at all. Pneumonic infiltrates, which appear in many cases, are frequently migratory and sometimes are associated with small pleural effusions. There may be a micronodular pattern resembling ground glass on the roentgenogram. Among the most characteristic evidences are those of basal pneumonitis with focal atelectasis and diaphragmatic elevation. In addition to the abnormalities produced by the lesions of the disease itself, secondary bacterial infection may further complicate both the clinical and the roentgenologic patterns. The outstanding features are those of migratory pneumonitis with basal linear shadows and pleural effusions sometimes accompanied by pericardial effusion. The following case report contains many of the features described.

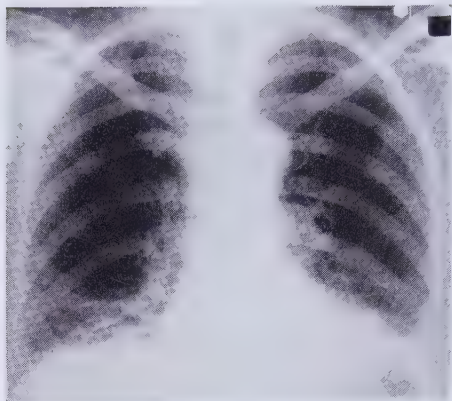


Figure 1 (Case 1). Infiltrative process in both lung bases with linear atelectasis on right and bilateral pleural effusions. (From Divertie, M. B., Brown, A. L., Jr., Witten, D. M., and Bulbulian, A. H.: Pulmonary manifestations of systemic diseases. *Postgrad. Med.* 34: 73-82 [July] 1963.)

CASE 1. A 59-year-old housewife was seen because of aching, swelling, stiffness, and redness of migratory type in the peripheral joints, involving principally the toes, ankles, knees, shoulders, elbows, wrists, fingers, and temporomandibular articulations. For a year before her visit she had been unable to close her fist tightly, open cans, or carry out fine movements. Her general health had been good otherwise, except for anorexia during the time that the joints had given the most trouble. Hot baths had been of benefit.

On examination there was minimal limitation of the motion of the elbows, the left shoulder, and both ankles. Her grip was poor and she had right olecranal bursitis. Fusiform swelling of the proximal interphalangeal joints was noted, and the wrist joints were tender and limited in their mobility. Apart from erythrocyte sedimentation of 65 mm. in one hour, none of the results of laboratory tests was abnormal. A diagnosis of rheumatoid arthritis was made and a program of physical therapy was prescribed for application at home. Because of an equivocal finding on the L.E. clot test, the patient was advised to avoid direct sunlight.

She spent most of the succeeding two years confined to her home, disabled and restricted in her activities. Exertional dyspnea had become prominent, and low-grade fever persisted. Intermittent left-sided pleuritic pain occurred, but thoracic roentgenograms showed no abnormality. Nosebleeds became a daily problem. Cortisone was given briefly, but symptoms returned when it was discontinued. Throughout the two years there were transient episodes of hives, and urticaria followed blood transfusions elsewhere. It was thought that these lesions did not represent lupus erythematosus, but rather that they were most probably due to hypersensitivity. She consulted her local physician because of weakness and poor appetite, and was found to have marked anemia and a prolonged bleeding time.

On reexamination at the Mayo Clinic, the patient appeared chronically ill and very weak. Arthritis involved multiple joints. A large area of the abdominal skin was mottled, and there was tenderness in the right upper quadrant. On auscultation, rales were heard at both lung bases and breath sounds were fainter than normal.

A chest roentgenogram showed pneumonitis and linear atelectasis above the right hemidiaphragm with elevation of the diaphragm on that side. There was pneumonitis in the left costophrenic angle. Fluid was present in both pleural spaces (Fig. 1). The gallbladder was nonfunctioning, but the evidence from excretory urograms was essentially normal with good concentration of the dye.

There were grade 1 red blood cells and grade 3 white blood cells (on the basis of 5) present in the urine. Hemoglobin measured 10.9 gm./100 ml. blood and leukocytes numbered 4800 per cu. mm., with lymphocytes 34 per cent, monocytes 3,

neutrophils 58, and eosinophils 5. Erythrocyte sedimentation was 124 mm. in one hour. The result of an L.E. clot test was positive. Bromsulphalein dye retention was 8 per cent at the end of 45 minutes. A special blood smear showed grade 3 rouleaux formation (on the basis of 4) with occasional myeloid immaturity. No cryoglobulins were found. The result of a tuberculin test was negative. Blood urea values were within normal limits. Examination of pleural fluid removed by thoracentesis was not helpful, simply confirming that it was an exudate.

RHEUMATOID ARTHRITIS

Another systemic disease is rheumatoid arthritis, whose main impact is on the musculoskeletal system. The lesions which involve the synovium and capsules of the joints are responsible for the characteristic migratory polyarthritis. Rheumatoid arthritis is three times more common in females than in males, and a genetic predisposition toward its development has been shown.⁴ Nonarticular lesions are essentially granulomatous and occur particularly in the heart, lungs, blood vessels, muscles, ocular tissues, and lymphoid system. Rheumatoid vasculitis is a frequent necropsy finding, and in many instances the microscopic appearance is closely similar to that seen in polyarteritis.²²

Synovial punch biopsy has proved most helpful in establishing the diagnosis, and microscopic examination of the specimen can reveal foci of lymphocytes and plasma cells. In recent years a number of serologic tests also have proved useful in the diagnosis of rheumatoid arthritis. They depend on the presence of a rheumatoid factor in the serum of patients with the disease. This factor has been shown to be a gamma globulin with the high molecular weight of the 19-S macroglobulins, and the tests depend on its ability to combine or react with immune or gamma globulin of normal 7-S size.²⁴ None of these tests is ideal in specificity and sensitivity, but they are of considerable interest in relation to the possible presence of immunologic abnormalities.

Attention was first drawn to involvement of the lungs in 1948 by Ellman and Ball, who reported three cases in which the classic manifestations of rheumatoid arthritis appeared to be associated with extensive pulmonary disease. In the two cases in which necropsy material was obtained, chronic fibrosing pneumonitis was present. While these changes were nonspecific, another report identified necrobiotic nodules in the lungs as well as in other tissues.³⁴

In a recent review of 27 cases of extensive pulmonary disease and rheumatoid arthritis which met the criteria established by the American Rheumatism Association, the histopathology in the lungs was found also to be nonspecific.⁵ Males exceeded females in the ratio of 2:1 and the lung disease preceded the rheumatoid arthritis in three of the 27 cases. In the remainder, the joint symptoms preceded the pulmonary disease or the onset of the two was simultaneous. Cough, dyspnea, and pleuritic pain

were the most frequent symptoms; and repeated simultaneous exacerbation of joint and lung disease occurred. The roentgenographic evidence was that of a soft, fluffy, patchy infiltrate, predominantly in the bases at first but later spreading to involve the entire lungs on both sides with extensive pulmonary fibrosis. Although cystic changes were seen occasionally, a typical honeycomb appearance was not encountered in this group of patients.

Pleurisy with effusion has been relatively frequent in patients with rheumatoid arthritis, and often has been persistent and refractory to the usual forms of treatment. Carr and Power noted that in this disease the glucose content of the pleural fluid was low or entirely absent. The significance of this interesting finding is not yet apparent. The interstitial fibrosis present in the lung is indistinguishable from the nonspecific changes seen in other types of diffuse pulmonary fibrosis. A nodular form of fibrosis of the lung, reported in coal miners, is considered distinct from the accepted appearances of pneumoconiosis.⁸

CASE 2. A 53-year-old man was seen at the Mayo Clinic because of pains of seven or eight years' duration in both hands, the left ankle, and the neck. At intervals the joints had become swollen, red, warm to the touch, and tender. These symptoms had been relieved by salicylates. Dry, nonproductive coughing, occasionally in paroxysms, had developed in the three months before his visit. Walking three to four blocks at normal pace or climbing one flight of stairs had been enough to produce shortness of breath and general fatigue.

On examination here, synovitis of minimal degree was present over the metacarpophalangeal joints of the left hand and the proximal interphalangeal joints of the right hand. There was swelling of the right wrist and limitation of movement of the right shoulder and stiffness of the neck. Many dry crackling rales were present in the lower two-thirds of both lung fields.

The patient was given instruction in physical therapy and advised to continue with his salicylates and with extra rest. Urinalysis showed specific gravity of 1.009, acid reaction, grade 1 hyaline casts, and grade 1 pyuria. The hemoglobin value was 12.4 and the leukocyte count 9100, with differential of lymphocytes 11.5 per cent, monocytes 4.5, neutrophils 77, eosinophils, 6.5 and basophils 0.5. The result of an L.E. clot test was negative. Erythrocyte sedimentation was 45 mm. in one hour. The chest roentgenogram was interpreted as follows: "Extensive diffuse pathologic process in both lungs, more marked on the left. Cardiac enlargement. There is probable chronic pulmonary congestion." Roentgenograms of the left hand and left foot did not indicate abnormality. There was no free fluid in the pleural spaces.

The patient returned after two months of treatment on this conservative program. His joints had improved somewhat but his breathing was no better. Pain of pleuritic type had developed over the left chest, and he had a slight cough producing half an ounce of mucopurulent sputum per day. His appetite was fair but his muscular strength was subnormal. Moist rales were present in both lower lung fields, worse on the left side. His right wrist was tender. Motion at the temporomandibular joint was difficult. The small joints of both hands were swollen, tender, and stiff; and abduction of the shoulders was limited.

The hemoglobin value was 12.6 gm. Urinalysis disclosed specific gravity of 1.026, but the other results were similar to those at the first visit. Again the result of an L.E. clot test was negative. The thoracic roentgenogram was essentially unchanged from that taken previously, but the evidence of extensive bilateral pul-

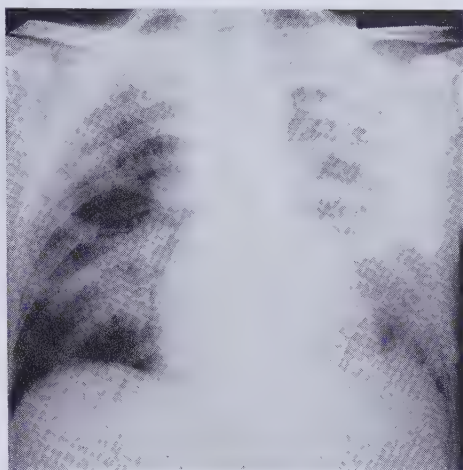


Figure 2 (Case 2). Extensive pathologic process in both lung fields with suggestion of honeycomb pattern and blunting of costophrenic angles. (From Divertie, M. B., Brown, A. L., Jr., Witten, D. M., and Bulbulian, A. H.: Pulmonary manifestations of systemic diseases. *Postgrad. Med.* 34: 73-82 [July] 1963.)

monary disease included a suggestion of a honeycomb pattern (Fig. 2). By this time, cultures of the gastric washings obtained at his first visit had been reported as negative for tubercle bacilli and fungi. Erythrocyte sedimentation was 63 mm. in one hour. Rheumatoid flocculation tests had not yet come into clinical use.

A biopsy of the synovial lining of the right wrist revealed "focal lymphocytic infiltration and fibrinoid degeneration compatible with rheumatoid arthritis." A lung biopsy disclosed "nonspecific chronic inflammation with fibrosis." Cultures of the lung tissue subsequently failed to produce a growth of tubercle bacilli, fungi, or any other organism. It was thought that this patient had chronic pulmonary interstitial fibrosis associated with his rheumatoid disease. He was dismissed with a conservative program and the prospect of using steroids at a later date.

POLYARTERITIS NODOSA

Men in the third or fourth decade of life are most frequently affected by polyarteritis nodosa. This diffuse necrotizing angiitis belongs to a group of diseases characterized by diffuse vasculitis whose relation to each other has not yet been clarified. Although originally called "periarteritis" nodosa and still often referred to by that name, it has come to be recognized as involving all three arterial coats to a much greater extent than the perivascular tissues.

It is a disease of small and medium-sized arteries with diffuse involvement throughout the body. The arteritis begins in the media and spreads to involve the intima and adventitia. The lumen may be occluded and an aneurysm may form. The varied systemic manifestations depend on the location and severity of the infarctions which develop beyond the site of thrombosis. When the respiratory tract is involved, the lesions may appear as granulomas with eosinophils present in large numbers; but the underlying pathology is still primarily vascular. Occasionally, necrosis is extensive and cavitation may simulate a pulmonary abscess, although the other

features of pulmonary suppurative disease are lacking. Gastrointestinal symptoms, renal and skin involvement, hypertension, polyneuritis, and polymyositis may occur in varying combinations. The diagnosis may be established by biopsy of muscle, testis, or other involved tissue.

In many instances, the disease follows a rapidly downhill course with death occurring in a few weeks or months of its onset. In others, however, the patients may strike a balance with their disease and continue to survive with remission and relapse for many years. Lung disease may precede the appearance of systemic features by an interval varying from a few months to several years. Rose and Spencer concluded that the total duration of the disease is considerably longer in patients with antecedent lung involvement, but that survival after the onset of systemic polyarteritis is shorter in such cases. The various reported forms of vasculitis involving the lung have confused the situation further.^{10, 16} Their relationship to polyarteritis and to each other is not yet clear.

The etiology of polyarteritis nodosa is not well understood, although its development shows some of the features of an auto-immune process. Supportive evidence of the allergic nature of the disease was reported when changes similar to those of polyarteritis were found in patients dying from serum sickness.³⁵ Also, the establishment of hypersensitivity in rabbits through the introduction of foreign serum has produced lesions that are similar histologically to those of this condition.³⁶ Since the disease continues to be active and frequently progressive after the suspected initial insult is removed, it has been suggested that the forbidden-clone hypothesis might be applied to explain the pathogenesis of polyarteritis nodosa.²⁷

The reported incidence of pulmonary involvement in polyarteritis nodosa has varied from 18 per cent to 29 per cent in different series.^{19, 41, 42} Cough, wheezing, occasional hemoptysis, and pleurisy with effusion are frequent when this occurs. If a patient first develops asthma in middle age, polyarteritis should be suspected and long-term steroid therapy should be seriously considered, especially if eosinophilia also is present.³⁹ Among 125 cases of microscopically proved polyarteritis nodosa, 30 per cent had peripheral eosinophilia in excess of 5 per cent of the total white blood count.¹⁴ The combination of peripheral eosinophilia with roentgenologic evidence of pulmonary infiltrates occurred in about 10 per cent of this number.

Apart from expiratory wheezing, physical signs in the chest were limited to scattered rales often located in the bases. A previous history of asthma was found to be most unusual, and in each instance the attack was the first the patient had suffered and had existed for more than two months without significant or lasting relief. Five of the patients died of renal failure during this attack and evidence of multiple-system disease was obvious in all of them. Purpuric lesions, mononeuritis multiplex, arthritic symptoms, and uremia were the most outstanding features. Hypertension was not

commonly found in these cases, presumably because of the rapid deterioration.

The roentgenographic appearances of the chest in this disease have been described as varied and nonspecific. Infiltrates, consolidations, cavities or abscesses, and pleural effusions may be evidenced. In the presence of peripheral eosinophilia, the migratory pneumonitis seen in some cases simulates the more benign Loeffler's syndrome, with which there is almost invariably a long background history of allergy and asthma. Other densities may appear softly nodular, and in some cases confluent and diffusely distributed throughout both lung fields. Cavitation, when present, may be of either the thin-walled type or the larger thick-walled variety more frequently seen in Wegener's granulomatosis. Intra-alveolar hemorrhage or necrotizing alveolitis appears as diffuse, confluent, soft nodules whose pattern simulates the butterfly distribution of pulmonary edema.³² Orthopnea and elevated venous pressures are usually absent when this complication occurs; and marked anemia, massive hemoptysis, and evidence of renal disease are almost invariably present. The following case illustrates the abnormalities described.

CASE 3. A 65-year-old man with no previous personal or family history of allergy or bronchial asthma was referred to the Mayo Clinic with a tentative diagnosis of Friedländer's pneumonia. Three months before admission, low-grade fever had developed with cough which produced a half cupful of yellow-green mucoid sputum daily. Because of increasing dyspnea and wheezing, he had been hospitalized elsewhere, and a roentgenogram had revealed an area of pneumonitis in the left upper lobe for which antibiotics had been prescribed. The patient's condition had improved, but within another few weeks he had begun to notice loss of weight and development of a purpuric eruption on both lower limbs. He had had transient diplopia with total but temporary blindness of the right eye. Anemia had been found, and pain had begun to affect the right calf with attendant numbness in the foot, which caused considerable difficulty in walking. Shortly before admission to the Mayo Clinic, hemoptysis had started.

On physical examination, the patient had low-grade fever and appeared chronically ill. Apart from a few scattered crepitant rales throughout both lungs, nothing significantly abnormal was heard on auscultation. Pulse rate and blood pressure were within normal limits. A purpuric eruption was present over the lower extremities, the right ankle jerk was absent, and dorsiflexion of the right foot was weak. Funduscopic examination revealed no gross abnormality. The neurologic deficit was thought to be consistent with a diagnosis of mononeuritis multiplex. The value for hemoglobin was 8.7 gm. and the leukocyte count was 14,100 with eosinophilia of 23 per cent. Erythrocyte sedimentation was 88 mm. in one hour. Blood urea measured 74 mg. per 100 ml. Urinalysis revealed specific gravity of 1.008, with acidity and grade 1 albuminuria and grade 3 microhematuria. Clinically, a diagnosis of polyarteritis nodosa was made, but biopsy of the left gastrocnemius revealed only normal muscle. Pneumonitis was manifested roentgenographically in the upper lobe of the right lung (Fig. 3).

Treatment was begun with cortisone and supportive blood transfusions. Despite this, the patient's condition deteriorated further. On the fourteenth hospital day, hemoptysis became profuse and coarse moist sounds could be heard throughout both lungs. Tachycardia and dyspnea increased considerably. Over the

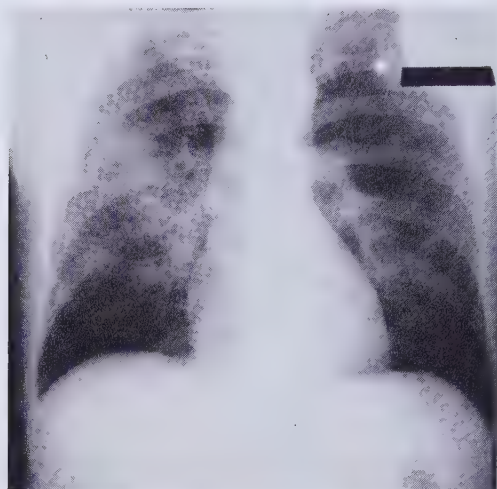


Figure 3 (Case 3). Pneumonitis in right upper lobe. (From Divertie, M. B., and Olsen, A. M.: Pulmonary infiltration associated with blood eosinophilia (P.I.E.): A clinical study of Loeffler's syndrome and of periarteritis nodosa with P.I.E. syndrome. *Dis. Chest.* 37: 340-349 [Mar.] 1960.)

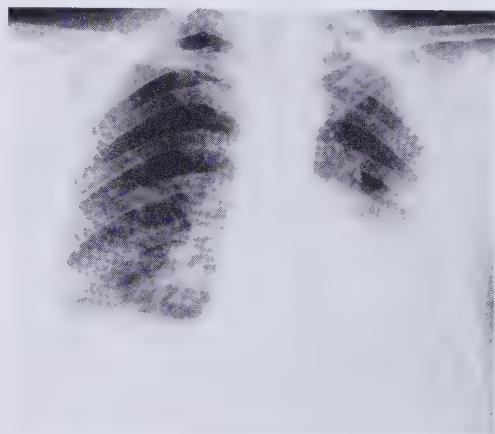


Figure 4 (Case 3). Evidence of diffuse soft nodules in both lung fields, more marked in upper portions, especially on left. (From Divertie, M. B., and Olsen, A. M.: Pulmonary infiltration associated with blood eosinophilia (P.I.E.): A clinical study of Loeffler's syndrome and of periarteritis nodosa with P.I.E. syndrome. *Dis. Chest.* 37: 340-349 [Mar.] 1960.)

next few days hemoptysis continued and further roentgenologic study showed bilateral patchy infiltrates in both lungs, interpreted initially as due to congestive heart failure (Fig. 4). Blood urea rose to 198 mg. and creatinine to 3.5 mg. per 100 ml. The urinary and other laboratory findings remained similar to those on admission.

The patient's condition improved clinically, but it was suspected that pulmonary roentgenologic changes represented necrotizing alveolitis rather than edema. On the twentieth hospital day he had a convulsion, passed into coma and rapidly died. At necropsy, typical lesions of polyarteritis were identified in the kidneys, abdominal viscera, muscles, and brain. The immediate cause of death was an infarct in the right occipital lobe. Changes compatible with necrotizing alveolitis were present in both lungs.

SCLERODERMA

A sclerotic indurative process affecting the connective tissue of many

regions of the body, scleroderma is seen more frequently in females than in males and occurs most often in the fourth and fifth decades of life. Characteristic skin changes are seen in all patients with the disease, but occasionally involvement of other organs precedes these changes by a variable length of time.

Because of the widespread involvement of body tissues, "progressive systemic sclerosis" or "visceral scleroderma" have been recommended as preferable to "scleroderma" alone, although the latter no doubt will continue in habitual use. It has been suggested that either a quantitative or a qualitative alteration in the ground substance may be present in this disease.^{13, 30} No chemical or structural defects of collagen have been demonstrated, and the principal morphologic abnormality appears to be an increase in the number of collagen fibers present. There is a remarkable tendency for calcium salts to be deposited in the affected tissues. The relationship of this condition to dermatomyositis remains undecided.

The lung takes part in the generalized process of fibrosis and thickening, and fibrosis of the alveolar walls is the most prominent microscopic pulmonary feature of this disease. Large areas of parenchyma become fibrous, with only occasional alveolar spaces recognizable. At a later stage cystic cavities—many of them subpleural—develop in a substantial number of patients.³¹ Vascular changes similar to those in other organs may be found also.

Clinically, an edematous phase may precede other evidence of the disease; but in many instances it does not occur. Induration and later atrophy are the commonest abnormalities. The three stages may be present at one time. Biopsy of the skin or other affected tissue is the most satisfactory method for establishing the diagnosis. The entire gastrointestinal tract, the myocardium, the kidneys, and the lungs may all be involved with symptoms appropriate to each. In addition, arthralgias, muscular weakness and atrophy, and osteoporosis with bony atrophy of the digits may be found. Raynaud's phenomenon is common.

The evidence for an immunologic disturbance in scleroderma is not well established at the time of writing. The disease has been found associated with hemolytic anemia,¹⁷ hypothyroidism of uncertain cause,²⁹ Hashimoto's thyroiditis,²⁷ and Sjögren's syndrome,⁶ in all of which immunologic disturbances have been suggested or proved. Circulating auto-antibodies have been demonstrated in a few cases and antinuclear antibodies have appeared, despite a negative result from the L.E. cell test.³ The antinuclear globulin is nonspecific, and further work is necessary to determine whether it is present regularly in the serum of individuals with active scleroderma.

In the majority of instances, pulmonary changes follow those in the skin; but at times they may be present at the beginning of the disease process and precede more generalized lesions by a varying period.⁴⁰ Minor changes in pulmonary function are found even in the absence of other

evidence of lung involvement. On the other hand, x-ray abnormalities can occur in patients having no pulmonary symptoms. Cough, dyspnea, and a variable amount of mucopurulent sputum are frequently the primary features of attendant lung disease. At a later stage pulmonary hypertension and right-heart failure may develop. The cardiac involvement often damages the myocardium so much that congestive failure supervenes before evidence of cor pulmonale has time to develop.¹¹ Physical findings in the chest are few—scattered rales, most frequently at the bases. Recurrent pulmonary infections are relatively common, and aspiration pneumonitis may result from sclerodermatous involvement of the esophagus. Except in the edematous phase of scleroderma, pleurisy and pleural effusions are rare.

In some cases involvement of the wall of the thorax by the fibrotic process interferes with respiratory excursion, and a restrictive type of ventilatory defect follows. In others, development of areas of compensatory emphysema may contribute features of obstructive ventilatory disease. Classically, thickening of the alveolar walls produces a diffusion defect with small lung volumes, peripheral arterial oxygen desaturation, hyperventilation, and abnormal carbon-monoxide diffusing capacity. In these cases the alveolar-arterial oxygen tension gradient is increased. Arterio-venous shunting within the lung may contribute to this abnormality also. Various combinations of defects of respiratory function may occur in a single patient.

The thoracic roentgenogram demonstrates abnormalities of infiltrative, fibrotic, or cystic type or a mixture of these.³¹ The changes are more marked in the bases of the lungs; the apices, as a general rule, are spared even in advanced stages of lung involvement. Fibrosis may appear as a diffuse and extensive process in which calcinosis may or may not be present. In other instances, fibrotic stranding extending to the bases or nodulation may be marked. Large areas of consolidation frequently are due to super-added pneumonia, sometimes caused by aspiration from a diseased esophagus. Cystic changes are often subpleural; rarely they are extensive enough to produce a honeycomb appearance of the lung.

CASE 4. A 40-year-old man, when first examined at the Mayo Clinic, reported having had symptoms of Raynaud's phenomenon for two years. Infection had developed in the tips of two fingers of the left hand and one finger of the right hand after exposure to cold, and healing had been slow. For one year before his visit, the skin of his hands, arms, neck, and chest had been tight to the point of interfering with movement. The legs and toes had been affected similarly but less severely. Some dyspnea had been noted on climbing stairs, and in the preceding month soreness of the tip of his nose had developed. In the six months before registration he had noted some sticking of solid foods on swallowing. For 18 years he had had symptoms of epigastric gnawing and heartburn, worse in the spring and fall, which had been relieved by mild alkali powders. Two years before admission he had noted that his stools were tarry.

On physical examination the entire trunk and the upper and lower limbs appeared hidebound, the skin seeming waxy and inelastic. The fingers and hands

were cold and there were scars on the second and third digits of each hand. The subcutaneous tissues felt doughy. Grip was poor. There was maceration and scaling between the toes.

The hemoglobin value was 15 gm. and the leukocyte count 11,900. Serum calcium was 10.2 mg./100 ml. and phosphorus 3.8 with alkaline phosphatase of 3.5 Bodansky units. A chest x-ray showed slight prominence of the left ventricle and some increase in bronchovascular markings in the lower parts of both lungs. An x-ray of the esophagus and stomach revealed a duodenal ulcer.

Returning one year later, the patient reported that there had been slow progression of his symptoms, especially in the tightness of the skin of the feet, thighs, and groins. Persistent heartburn was now most troublesome to him and midabdominal pain would follow immediately after ingestion of a meal, with regurgitation of hot sour food into his throat. His stools had become soft and for one day each week he had diarrhea. Antacids, milk, and foodstuffs aggravated his distress instead of relieving it. There had been one episode of typical duodenal-ulcer pain. He had lost 18 pounds during the preceding six months.

Examination revealed dermatitis of the scalp and generalized scleroderma with deep pigmentation most marked over the abdomen. The mouth opened to only 40 per cent of maximum. The skin of the genitalia showed scleroderma, along with the other areas previously affected. The feet turned blue on exposure to room air.

Urinalysis revealed specific gravity of 1.025 with an acid reaction. Microscopically the specimen appeared normal. The hemoglobin value was 13.1 gm., the leukocyte count 12,100 and the erythrocyte count 3,800,000 per cu. mm. of blood. A diffuse process was evidenced roentgenographically in the bases of both lungs and was more marked on the right (Fig. 5). These findings were compatible with involvement by the systemic disease. The colon appeared normal roentgenologically but the small bowel showed changes thought to be due to scleroderma. Changes were revealed in the esophagus also and were considered due to scleroderma.

The patient was last heard from two years after his second visit. On a regimen of antacids and supportive care, he was living remarkably well with his disease. The chest involvement was troublesome, mainly because of limiting his activities by dyspnea.

A thorough discussion of the treatment for these connective-tissue diseases is not to be attempted in this presentation. The pulmonary

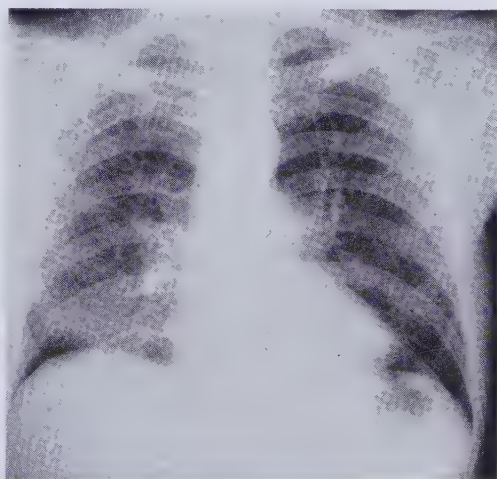


Figure 5 (Case 4). Pathologic process in both lung bases, more obvious on right. (From Diver-tie, M. B., Brown, A. L., Jr., Witten, D. M., and Bulbulian, A. H.: Pulmonary manifestations of systemic diseases. *Postgrad. Med.* 34: 73-82 [July] 1963.)

disease which may complicate each one of them may respond to the basic treatment given. In addition, a general program of prophylaxis is important. The patient should be cautioned to avoid any irritant to his respiratory tract and to seek attention promptly if an infection develops in it. Adequate fluid intake and a warm, dry climate may be of benefit; and until positive proof is available that influenza prophylaxis is not of value, it seems best to recommend that. A long-term antibiotic program similar to that established for patients with emphysema and asthmatic bronchitis may be of value to these individuals also.

CONCLUSION

The connective-tissue disorders—and their relationship to each other and to basic immunologic processes in the body—are of great importance to the physician. The thoracic manifestations of these diseases may be among the first to appear.

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Three Types of Pulmonary Involvement in Polymyositis

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While the pulmonary manifestations of the other collagen diseases have been well documented, only three cases of primary pulmonary involvement in dermatomyositis or polymyositis have been found reported in the literature.^{7, 10, 14} Apparently this complication is unusual. Recently, two additional cases were described in which the clinical pattern was that of polymyositis but the authors considered the alterations in pulmonary function to be more suggestive of progressive systemic sclerosis.¹⁷

In our recent experience, three patients with polymyositis presented major pulmonary problems, each of a different type.*

REPORT OF CASES

CASE 1. A 63-year-old foreman of a department of public utilities was admitted to the Mayo Clinic on December 12, 1962, with the chief complaint of progressively increasing dysphagia of nine months' duration. Probably his illness had been first manifested by difficulty in reaching the brake pedal of his truck two years before admission. Eighteen months before admission he had noted generalized weakness, anorexia, loss of weight, and difficulty in coughing and clearing mucus from his respiratory tract. The dysphagia was most noticeable on swallowing meat. Though he swallowed carefully, he still coughed frequently while eating.

Nine months before admission a diagnosis of amyotrophic lateral sclerosis had been made elsewhere, and the patient had been treated for several months with ACTH. He reported temporary improvement, although his attending physician had not recognized any.

One month prior to admission pneumonia had developed, requiring hospitalization and antibiotic therapy. The patient had become progressively weaker and dyspneic and had lost weight. There was no history of muscular pain or skin rash.

* Examination of tissue sections was done by Dr. George P. Sayre, Section of Experimental and Anatomic Pathology.



Figure 1 (Case 1). Evidence of aspiration pneumonia, most prominent in right base.

On examination he appeared weak and elderly, and the recent loss of weight (which had amounted to 54 pounds in 18 months) was obvious. The blood pressure was 114 mm. Hg systolic over 80 diastolic, and the pulse rate was 116 beats per minute. The patient was having difficulty in clearing the secretions from his pharynx. His cough was weak. Auscultation of the lungs revealed rhonchi in the lower portion of the right lung. The neurologic examination demonstrated marked muscular weakness and atrophy of shoulder and pelvic girdle muscles, the latter being weakest. The muscles of the hands and feet were strong. The deep tendon reflexes were normal and there were no pathologic reflexes.

Among laboratory studies urinalysis gave normal findings. The hemoglobin was 13.2 gm./100 ml. blood, the leukocyte count 9600 per cubic mm., and the erythrocyte sedimentation 80 mm. in one hour (Westergren method). Response to the VDRL test was nonreactive. Urea measured 54 mg./100 ml. blood, the serum glutamic oxalacetic transaminase (SGOT) 1.7 micromoles/hr./ml. serum (normal up to 1.43). Thoracic roentgenography demonstrated a pneumonic process in the basilar aspects of both lungs (Fig. 1). Examination of the esophagus was not possible, for the barium mixture was aspirated into the trachea on attempted swallowing.

Electromyography revealed normal conduction velocities of the left ulnar and median nerves but slightly subnormal velocity in the left peroneal nerve. Needle-electrode examination of muscles in the upper and lower extremities showed a uniform pattern. At rest there were fibrillation potentials of grades 1 and 2 and no fasciculations. On voluntary contraction the number of motor-unit potentials was increased in comparison with the strength of contraction, with duration short and amplitude low. The proportion of polyphasic potentials was high. The electromyographic findings were interpreted as being compatible with a diagnosis of polymyositis.

A clinical diagnosis of polymyositis was made. However, the immediate problems were the aspiration pneumonia and inability to maintain adequate nutrition. Gastrostomy was established without difficulty, and feedings amounting to 2500 calories per 24 hours were given. Prednisone in a dose of 10 mg. four times daily was exhibited. On this program the patient improved appreciably, as he did not have to struggle with the aspirated food at each meal. He was dismissed to continue taking the corticosteroid and physiotherapy at home.

He returned for re-examination two months later and reported that his strength was about the same. He had had no further difficulty with pneumonia. The stoma

was functioning well. He had gained some weight but was not able to swallow better. He was taking 20 mg. of prednisone per day in divided doses. Physical examination demonstrated some progression of the weakness of the trapezius muscles, but muscular strength generally was unchanged. The thoracic roentgenogram revealed only residual fibrosis in the basilar areas. The results of laboratory studies were the same except that the sedimentation now was 25 mm. in one hour and the SGOT value was 4.34 micromoles. Since there had been no apparent improvement in muscular strength, gradual reduction of the dose of prednisone to 5 to 10 mg. per day was advised.

The patient died at home on May 25, 1963, apparently as a result of pneumonia. Tissue sections from the lung were reviewed here and showed the changes of chronic aspiration pneumonia with considerable fibrosis. Sections of trunk muscle showed extensive degeneration of muscle fibers with associated hyperplasia and hypertrophy. There was some evidence of regeneration and a few scattered areas of active degeneration with mild inflammatory reaction. Sections of diaphragmatic muscle were involved similarly but showed more active degeneration. Although not classic, the changes were considered consistent with polymyositis.

This is a case of chronic polymyositis in which dysphagia and resultant aspiration pneumonia became the major problems. Of course, aspiration pneumonia is not unique to patients with polymyositis. It is a common problem in patients with neuromuscular involvement of pharyngeal muscles or high esophageal obstructing lesions, and in those whose protective cough mechanism is depressed from any cause—as, for example, in disturbances of consciousness or muscular weakness.

Death was postponed in this case by the gastrostomy, which enabled the patient to maintain nutrition and avoid more pneumonia for a short while. It is known that he continued to attempt to swallow food at times even after the gastrostomy. Perhaps had he refrained completely from swallowing food, the pneumonia which was the immediate cause of death could have been postponed longer. The higher SGOT value at the time of his second admission suggests that the polymyositis had flared and was not controlled by the dose of prednisone administered.

CASE 2. A 65-year-old housewife was admitted to the hospital critically ill on September 17, 1962. Relatives said that she had begun having difficulty in swallowing $2\frac{1}{2}$ years prior to admission. Although the results of several roentgenographic examinations of the esophagus with barium elsewhere had been reported as normal, she had continued to choke when swallowing. The relatives reported that she had had painless "swelling" of the knees and to a lesser extent of the ankles, which they had attributed to "arthritis." Difficulty in climbing stairs had required her to pull herself up by the handrail. During the week prior to admission here her condition had worsened rapidly and she had had to be hospitalized elsewhere. Because she had become very nervous, imipramine had been administered. The weakness had increased, breathing had been difficult, and cyanosis had appeared. She had lost 35 pounds during the nine months before admission.

On examination at the time of admission to an affiliated hospital, cyanosis was evident and the patient was lapsing into periods of unresponsiveness. There was generalized muscular twitching. The blood pressure was 110/70 and the pulse rate 120 beats per minute. The temperature was 98° F. Respirations were shallow at 20 per minute. The cervical veins were distended. Auscultation of the lungs pro-

Table 1. *Results of Acid-Base Studies (Astrup Technique) and Other Electrolyte Values, Case 2*

	Sept. 17, P.M.		Sept. 18	Sept. 19	Sept. 21	Sept. 24	Sept. 27	Oct. 1
	12:30	6:00						
pH (actual), venous blood	7.22	7.4	7.56	7.42	7.42	7.38	7.38	7.35
pCO ₂ (limits, mm. Hg), venous blood.....	106-122	68.2-74.0	43.1-47	58-67	60-68	70-79	64-73	73-80
Bicarbonate (standard), mEq./L. plasma.....	30.5	36.8	37	33	34.3	34.8	32.5	34
Base excess, mEq./L. blood.....	10	17	17	11.8	14.4	14.9	12.2	13.9
Buffer base mEq./L. blood.....	57.2	62.2	37	58	60	61	58.2	58.9
CO ₂ combining power, mEq./L. plasma.....	37		32	29				
Chlorides, mEq./L. plasma.....	88.8		87.4	94.6				
Sodium, mEq./L. serum.	149		139	133				
Potassium, mEq./L. serum.....	4.9		3.1	4.7		5.5		
Urea, mg./100 ml. blood.	98		62	33				
Level of consciousness...	Unresponsive	Responsive at times	Quite alert			Responsive		

duced normal breath sounds but percussion revealed diaphragmatic dullness at an abnormally high level. Cardiac auscultation disclosed a fixed splitting and accentuation of the second pulmonic sound. There was no peripheral edema and the joints appeared normal.

Findings on funduscopic examination were normal but there was weakness of the orbicularis oculi. There was also weakness of the pharyngeal muscles and tongue, and of the flexor muscles of the neck. There was minimal weakness of muscles in the left upper extremity. The greatest weakness was of the bilateral quadriceps and hamstring groups. The deep tendon reflexes were normal except for the quadriceps reflexes, which were absent.

In laboratory studies carried out during the period of emergency treatment, the hemoglobin measured 14.7 gm. and the leukocyte count was 7200, the differential being lymphocytes 13 per cent, monocytes 1, neutrophils 85, and eosinophils 1. Erythrocyte sedimentation was 9 mm. in one hour. Response to the VDRL test was nonreactive. Urinalysis disclosed proteinuria of grade 1 (extreme being grade 4), a few hyaline casts, and a few red cells. Results of acid-base studies by the Astrup technique¹ and other electrolyte values are recorded in Table 1.

The thoracic roentgenogram made at the time of admission showed prominent bronchovascular markings in both bases (Fig. 2). The admission electrocardiogram revealed a sinus rhythm of 150 beats per minute, prominent P waves in lead II, and T-wave inversion in leads II and III and V₃₋₆.

While these laboratory data were being awaited, it was suspected that the patient was in respiratory acidosis due to hypoventilation as a result of some muscular disease such as polymyositis or myasthenia gravis. Administration of 1 mg. of neostigmine (Prostigmin) intramuscularly did not increase the muscular strength. Oxygen was given cautiously by mask and she promptly became apneic and unresponsive. Respiration then was assisted with a mechanical respirator and face mask until a tracheostomy utilizing a cuffed tracheostomy tube was established, and ventilation was maintained thereafter by an intermittent positive-pressure breathing (IPPB) machine under control of the automatic cycling device.

An effort was made to improve the patient's ventilation gradually, thus avoiding the hazards of rapid correction of the hypercapnia and respiratory acidosis

(pH of 7.22 and pCO_2 of 106 to 122 mm. Hg). After six hours of controlled ventilation the pH was 7.4 and the pCO_2 had been reduced to between 68.2 and 74.0 mm. Hg. However, immediately after ventilation was improved, she became hypotensive and remained unresponsive. The sensorium cleared gradually over a period of 18 hours. Intravenous vasopressors were needed for 36 hours to maintain the blood pressure at normal values. Astrup studies on the second day disclosed primarily a metabolic alkalosis with hypokalemia for which potassium chloride was administered through a nasogastric feeding tube.

The patient was digitalized when first seen here. On the following day the venous pressure and the second pulmonic sound were normal. The electrocardiogram then showed a nodal rhythm with deeper T-wave inversion. Subsequently, normal sinus rhythm was restored and the T waves became normally upright.

On the day after admission an electromyogram made by Dr. E. H. Lambert demonstrated a marked abnormality. There were many fibrillation potentials in the muscles of the right upper and lower extremities. The motor-unit action potentials were almost all polyphasic with spikes of short duration. Conduction velocity of the nerves was normal and there was no evidence of a defect in neuromuscular conduction. The electromyogram was interpreted as showing an active myopathy of the type seen in polymyositis. The SGOT value was 4.88 micromoles. An electroencephalogram showed a generalized dysrhythmia, grade 3, probably due to a diffuse cerebral disturbance caused by electrolyte imbalance. Corticosteroid therapy was initiated with 100 mg. of hydrocortisone given intravenously and continued as 40 mg. of prednisone given daily in divided doses by feeding tube.

The patient's condition generally improved. Respiration again became spontaneous but ventilation had to be assisted with the IPPB machine except for short periods during which she sat in a chair. Pneumonia developed in the right middle lobe and was treated with penicillin and streptomycin. Muscular strength, however, did not improve demonstrably and she was unable to swallow when the feeding tube was removed after 10 days of corticosteroid therapy. At this time the SGOT value was normal. The patient's condition worsened gradually thereafter. Pneumonia recurred despite antibiotic therapy, tracheal suction, and continued support of ventilation. She died 17 days after admission.

At necropsy the body showed evidence of considerable wasting, especially loss of muscle in the lower limbs. The general examination revealed bilateral hydrothorax amounting to 500 ml., and both lungs were heavy with a moderate amount of congestion and nodularity, particularly in the lower lobes and the posterior parts of the upper lobes. Mucopurulent material was found filling the bronchi. The

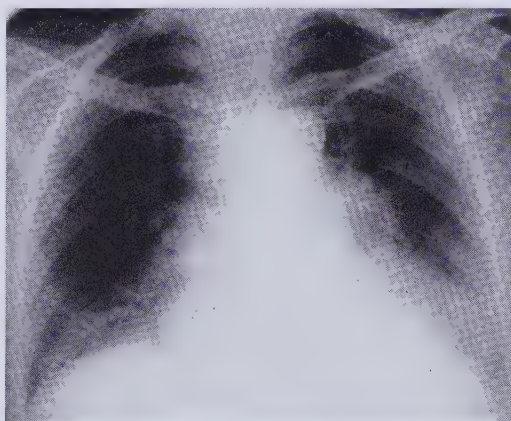


Figure 2 (Case 2). Prominent bronchovascular markings in both bases.

spleen was moderately enlarged and extremely soft, with hemorrhage into its substance. The heart was essentially normal, with minimal atherosclerosis of the coronary arteries. There was marked pallor and wasting of the bilateral triceps, quadriceps, and anterior tibial muscles. In the latter groups, it was difficult at first to distinguish muscle from deeper connective tissue.

Histologic examination of the lungs revealed diffuse hemorrhagic edema and atelectasis, most marked in the lower lobes, with foci of bronchopneumonia which were either older and organizing or more recent. Studies of the biceps and triceps muscles showed varying degrees of scattered hyaline degenerating fibers, a few fibers undergoing Zenker's degeneration with phagocytosis. Three intercostal muscles showed a varied pattern of atrophy with increased connective tissue, Zenker's degeneration, phagocytosis, and areas having basophilic fibers.

The quadriceps, gastrocnemius, and anterior tibial muscles contained areas of extreme atrophy and other areas where active degeneration of fibers was taking place. Both psoas muscles appeared normal. The pathologic diagnoses were polymyositis, bilateral bronchopneumonia, and hemorrhages into the spleen.

This is a case of chronic polymyositis in which the patient's main complaint during most of her illness was dysphagia but in which the acute problem that developed during the week before admission was ventilatory insufficiency (due to muscular weakness) and resultant respiratory acidosis. We might speculate that the polymyositis flared at this time with rather acute involvement of the respiratory muscles.

Very probably the extreme nervousness which she was said to have had in the week before admission was anxiety due to inadequate ventilation. Sedatives, which ordinarily might be given to an anxious patient, would only increase the inadequacy of ventilation and the CO_2 retention.

Apnea of the kind that followed the administration of oxygen occurs whenever the CO_2 tension is at or near such a level that a further increase does not stimulate but depresses the respiratory center. Thus, at the same time that the chemoreceptor drive from low oxygen tension was being removed by the administration of oxygen, the rise in CO_2 tension as hemoglobin became saturated evoked no respiratory drive. Chemoreceptor stimulation due to a fall in pH was insufficient to prevent cessation of respiration.

The muscular twitching observed initially is seen often in respiratory acidosis, and it disappeared with correction of the acidosis.

Rapid correction of a state of hypercapnia has caused cardiac arrhythmias, including fatal ventricular fibrillation, in laboratory animals.^{21, 23} Also, it has been postulated that the sudden deaths sometimes seen immediately or shortly after tracheostomy may be due to a rapid fall in pCO_2 when ventilation is improved.^{5, 9} If the respiratory acidosis is caused by diffuse obstructive pulmonary emphysema, the basic disease process in the lungs often makes it impossible to achieve a rapid reduction of pCO_2 . In a case like the one reported here, however—where the ventilatory capacity of the lung itself is presumably normal but the muscular power to operate the bellows mechanism is lacking—alveolar ventilation can be rapidly improved and the pCO_2 sharply lowered by simply using a mechan-

ical respirator. Therefore one must exercise caution to ensure that the increase in alveolar ventilation is gradual. Despite our efforts to do this, the patient still became hypotensive as the hypercapnia was reduced; and she remained so for 36 hours despite normality of $p\text{CO}_2$ and pH. Although hypotension occurs as a result of respiratory acidosis²² and has been seen in some of the cases of sudden collapse following tracheostomy, it appears that such duration as this is unusual. However, Buckley and associates found hypotension lasting as long as 48 hours in patients who had developed severe hypercapnia during anesthesia.

Administration of stimulants for the respiratory center, which may be useful in treating respiratory acidosis due to other causes,^{8, 13} would have been illogical in this case because the muscles of respiration were incapable of responding to stimuli from the respiratory center.

It cannot be determined whether the nodal rhythm that prevailed during the second day of treatment was related to the reduction of the hypercapnia, digitalis therapy, or a combination of factors. The evidence for pulmonary hypertension and early right ventricular failure was definite, and these disorders were attributed to hypoxia¹¹ and acidosis.² The dramatic disappearance of these signs probably was due to correction of the hypoxia and not to digitalis therapy. No significant cardiac lesions were found at necropsy.

Although this patient was only semicomatose before treatment was instituted, she became completely comatose during the time that the $p\text{CO}_2$ was being restored to nearer normal values. The explanation for this is not clear, although it is known that the cerebral symptoms of respiratory acidosis and hypercapnia may persist beyond correction of the abnormalities.²² Perhaps a factor in the phenomenon is chemical changes in extracellular and intracellular fluids induced by correction of the acidosis.

The choice of the type of respirator to be used in such a case depends upon the experience of the physician. A tank-type respirator would have improved alveolar ventilation as well as the one we employed. Tracheostomy still would have been necessary, although the inflatable cuff would not have been needed. The IPPB machine used here with automatic control of the cycle worked very well and allowed us to carry out the diagnostic procedures, routine nursing care, and intravenous fluid therapy with greater ease than if the patient had been in the tank respirator. The inflatable rubber cuff on the tracheostomy tube, which when inflated occludes the lumen of the trachea and makes the system relatively airtight, must be deflated for a few minutes every hour to avoid pressure necrosis of the tracheal mucosa.

As the Astrup data in Table 1 indicate, the $p\text{CO}_2$ values were not maintained so near normal after the patient resumed control of her respiration as when ventilation was controlled automatically. Mechanical assistance to breathing was used at irregular intervals during this period, and the collection of blood for Astrup studies did not always coincide with the

changes to and from assistance. Terminally, secretions also probably interfered with air exchange. The range of $p\text{CO}_2$ noted was considered satisfactory, although it cannot be stated with absolute certainty that hypercapnia does not somehow interfere with the therapy of polymyositis.

Twenty-four hours after ventilation had been improved by means of the mechanical device used, a state of metabolic alkalosis with hypokalemia developed. The occurrence of metabolic alkalosis following correction of chronic hypercapnia or compensated respiratory acidosis is well documented. The rationale for it is that during respiratory acidosis potassium diuresis occurs, with associated loss of potassium from the cells. As the acidosis is corrected, extracellular potassium shifts to the intracellular compartment, producing a hypokalemic state which requires the administration of potassium and chloride for correction.^{12, 20} Antecedent diuretic and corticosteroid therapy may promote a potassium loss and foster the development of hypokalemia in this type of patient.^{4, 16} To our knowledge the patient had not received such drugs. However, the inadequacy of her dietary intake may have been a factor in promoting a potassium deficit prior to the institution of therapy for respiratory acidosis.

The histologic findings in the muscle were compatible with those of the chronic diffuse type of polymyositis. There was very little evidence of regeneration. The varied pattern seen in the different muscles is a common finding in this disease. It is probable that studies of all intercostal muscles and the diaphragm would have shown involvement similar to that seen in three intercostal muscles, which would explain the respiratory insufficiency. Problems in maintaining adequate ventilation are not uncommon in other neuromuscular disorders such as myasthenia gravis, poliomyelitis, amyotrophic lateral sclerosis, and neuronitis. However, it is unusual for the involvement in polymyositis to be so extensive that adequate ventilation cannot be maintained.

CASE 3. A farmer's widow, 56 years old, was admitted to the hospital with the primary complaint of progressive dyspnea of six months' duration. She had been well until nine months before admission when "arthritis" had developed in both shoulders, elbows, wrists, proximal interphalangeal joints, and knees. She recalled having had pain, swelling, and morning stiffness. Injections of cortisone had helped. Ten weeks before admission she had begun coughing and expectorating clear mucus. Elsewhere, a roentgenogram had been interpreted as showing viral pneumonia, for which she had been hospitalized. She had continued to have a fever of 102 to 103° F. each afternoon. During this illness she had lost 30 pounds.

On examination she appeared somewhat obese and moderately ill. The blood pressure was 100/56 and the pulse rate 104 per minute. The temperature was 101° F. Auscultation disclosed inspiratory rales over the lower half of each lung. There was a short pulmonic systolic murmur. Slight synovial thickening and increased temperature were found in the wrists, metacarpophalangeal joints, and knees. Small effusions also were apparent in the knees. There were no skin changes to suggest scleroderma or the cutaneous component of dermatomyositis.

The neurologic examination revealed moderate weakness without atrophy of the proximal or shoulder and pelvic girdle muscles.

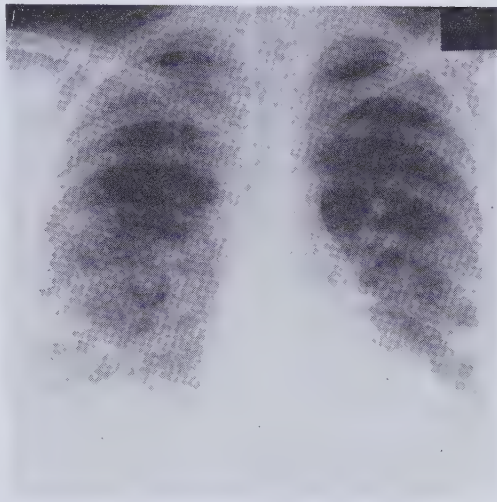


Figure 3⁷(Case 3). Bilateral patchy and confluent densities, most prominent in lower halves.

Among laboratory studies, urinalysis gave normal findings. The hemoglobin measured 10.6 gm. The leukocyte count was 5400 with a normal differential. Response to the VDRL test was nonreactive. The fasting blood sugar was 62 mg./100 ml. (normal: 65 to 90), and the blood urea 20 mg./100 ml. Erythrocyte sedimentation was 73 mm. in one hour (Westergren) and the SGOT was 2.44 micromoles/hr./-ml. Response to the flocculation test for rheumatoid factor was reactive; the L.E. cell preparation was negative. Roentgenography of the thorax disclosed a patchy pathologic process throughout both lungs (Fig. 3). There was no free pleural fluid. Cultures of sputum and gastric content grew no pathologic bacteria or fungi. No malignant cells were found in the sputum. Results of the second-strength tuberculin (250 T.U.), histoplasmin, and coccidioidin skin tests were negative.

Electromyographic studies revealed normal conduction velocities of the right ulnar, median, and peroneal nerves. In the right deltoid muscle, needle-electrode examination showed fibrillation potentials and low amplitude, short-duration motor-unit action potentials with an increased proportion of polyphasic potentials. The findings were interpreted as compatible with a myopathy. Biopsy of the right deltoid muscle revealed acute and subacute degeneration of muscle fibers consistent with a myopathy.

Studies of pulmonary function disclosed subnormal lung volumes, absence of obstructive phenomena, and a significantly low CO diffusing capacity (Table 2)—findings consistent with a restrictive type of defect.

Roentgenographic examination of the esophagus with barium revealed an abnormal motility pattern. This was confirmed by studies of esophageal pressure, which demonstrated contractions that were irregular in amplitude, duration, and timing. None of the contractions in response to deglutition were excessive in amplitude and some were quite weak. These findings were considered to be consistent with a neuromuscular disorder.

After the beginning of corticosteroid therapy (prednisone, 10 mg. every eight hours), the patient's strength improved very dramatically, she became afebrile, and the rheumatic complaints and joint manifestations disappeared. The erythrocyte sedimentation decreased to 23 mm. and the SGOT value decreased to 1.68 micromoles. She was dismissed to continue taking corticosteroids, together with antacids and potassium supplements, at home.

When she returned for re-examination two months later, she had been taking

Table 2. *Changes in Pulmonary Function in Polymyositis and Effect of Corticosteroid Therapy, Case 3*

FUNCTION	PREDICTED NORMAL	BEFORE THERAPY	10TH WK. THERAPY
Vital capacity.....	3.1 L.	1.4	2.08
Residual volume.....	1.2 L.	.99	.98
Total capacity.....	4.3 L.	2.39	3.06
Maximal breathing capacity.....	72 L./min.	32	67
Maximal mid-expiratory flow.....	> 1.7 L./sec.	1.7	2.2
Nitrogen washout index.....	< 2.5 per cent	.4	.6
Arterial oxygen saturation after 5 min. exercise.....	> 94 per cent*	97*	94†
CO diffusing capacity.....	22 ml./min./mm. Hg	8*	9†

* Utilizing low ($5\frac{1}{4}$ ") step.

† Utilizing normal (9") step.

20 mg. prednisone daily. No pulmonary symptoms remained, and muscular strength was normal. Examination of the joints showed no abnormalities. Mild changes of hypercortisonism were noted. Erythrocyte sedimentation was 55 mm. and the SGOT value was 0.67 micromole. The hemoglobin value was 13.8 gm., the leukocyte count was 7100, and the findings from urinalysis were normal. A roentgenogram of the thorax showed questionable lessening of the radiodensities. Re-evaluation of pulmonary function disclosed some increase in lung volumes and a definite increase in maximal breathing capacity, but no significant improvement in diffusion (although results of the two tests of diffusion cannot be compared exactly, since the exercise was more strenuous in the second test).

She was dismissed with advice to take extra rest and gradually diminishing doses of prednisone, and it was suggested to her physician that the SGOT values be used as indicators to possible flare-ups of her disease.

This is a case of acute polymyositis in which the major problem was dyspnea due to a bilateral pulmonary process. Although we do not have lung tissue for histologic examination, we believe that the pulmonary disorder most likely is interstitial fibrosis. The roentgenographic appearance and the functional derangement are consistent with such a process. Although the patient presented with some joint involvement and the rheumatoid factor was found to be present, it is considered that the primary disease process is polymyositis and not rheumatoid arthritis. The rheumatoid factor has been reported to be present in 50 per cent of patients with polymyositis, and joint manifestations in 30 to 50 per cent.^{18, 19} Corticosteroid therapy was of considerable benefit in respect to the joint and muscular disease, and it was attended by significant improvement in the lung volumes and maximal breathing capacity. The increase in vital capacity and maximal breathing capacity could be due to improved muscular strength as well as an actual improvement in the pulmonary disease process (Table 2). Of significance is the fact that the CO diffusing capacity had not improved.

COMMENT

The first two cases are examples of simple chronic polymyositis with no evidence of involvement of other systems. A discussion of why this should or should not be considered a collagen disorder is beyond the scope of this presentation. The pulmonary complications observed are not peculiar to polymyositis of this type, but are seen in any neuromuscular disease that affects the muscles of deglutition or ventilation. Dysphagia is a frequent symptom in polymyositis, and aspiration pneumonia the usual terminal event.⁶

Case 3 was a more complicated problem, presenting features of a widespread mesenchymal or collagen disorder.

Since nonspecific interstitial pneumonitis and fibrosis are witnessed in the other collagen diseases, it seems quite reasonable that the same pulmonary changes should be found in this type of polymyositis and that the pattern of functional derangement should be similar to that with the restrictive type of defect seen in patients having interstitial fibrosis due to other causes.

The subject of polymyositis cannot be discussed without reference to its association with malignancy. A recent study at this institution disclosed that seven of a group of 102 patients with polymyositis also had a malignant lesion.¹⁵ The authors pointed out that this incidence is lower than that usually mentioned in the literature. Necropsy excluded malignancy in the first two cases of this report and there has been no evidence of malignancy in Case 3.

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Cell Turnover in the Respiratory Tract*

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In recent years an increasing amount of attention has been given to the kinetics of cellular proliferation, both in experimental animals and in man, to increase the understanding of growth rates and rates of liberation of cells from zones of proliferation and of the factors which may influence these. Many studies have been made of the cell populations of the bone marrow and gastrointestinal epithelium, whose cell production—in the normal adult mammal^{1, 3-7, 11, 13, 14}—is the chief counterbalance to cell loss.

Two main methods have been used in studies of cellular proliferation.

1. Mitotic counting, with or without the use of colchicine or X-irradiation.
2. Radiolabeling of deoxyribonucleic acid (DNA) precursors and subsequent radioautography.

In the first method counts are made of the percentage of cells undergoing mitotic division, either in tissue sections or in smears. Usually this technique is combined with preliminary injection of the animal with colchicine, which arrests mitosis in metaphase, so that a count made four hours afterward will allow assessment of the number of cells which have attempted mitotic division during this time. From this it is possible to determine the rate of cell division and the turnover time. Mitotic duration also may be calculated, since the number of dividing cells at a given time in an animal treated with colchicine can be compared with that in an untreated animal. This method has been reviewed by Leblond and Walker; and the former, quoting elsewhere¹⁰ the work of Stevens Hooper, stated that for dependable results any untried sample of colchicine must pass three tests:

* This investigation was supported in part by Research Grant GM09623 from the National Institutes of Health, Public Health Service.

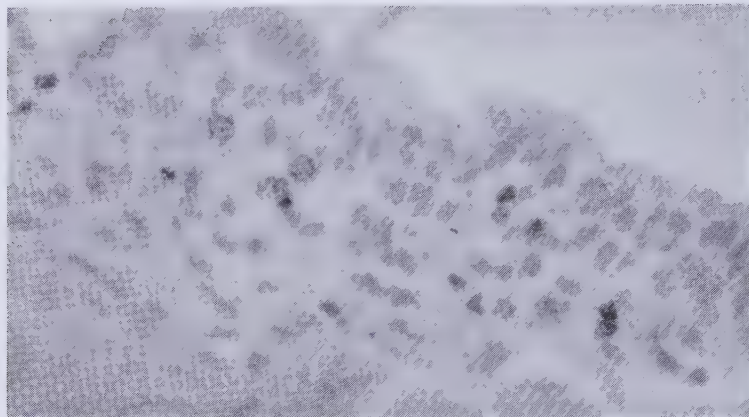


Figure 1. Labeling of nuclei in tracheal epithelium of mouse six hours after parenteral injection of thymidine- H^3 . (Radioautograph: Kodak AR 10 stripping film. Hematoxylin and eosin; $\times 600$.)

1. The drug must have no effect on mitotic stages preceding metaphase.
2. The time at which the drug takes effect must be known.
3. The effect of the drug should last several times as long as metaphase and longer than the experiment.

Knowlton and Widner have calculated mitotic duration by means of mitotic counting after X-irradiation of the cells. They assumed that the X-irradiation prevented cells from entering prophase but that any cells already in mitosis at the time of the irradiation would progress to telophase. The number of mitotic cells counted at different intervals after irradiation showed a rapid fall, and the authors reasoned that assumed mitotic duration—the time taken for all the mitotic figures to disappear—was the duration of the mitotic process. They used the results obtained from the calculations of mitotic duration and the mitotic index to determine the turnover time of various tissues in the mouse.

The second method, radiolabeling of precursors of DNA followed by radioautography, gives considerable information as to the movement of labeled cells during the period of study. Tritium-labeled thymidine is incorporated by the nuclei of cells synthesizing DNA (Taylor and associates); and since loss of the label occurs only through cell death or through dilution of successive cell divisions, it is an ideal tool for detection of labeled cells by radioautography. The assumption is made that labeled cells behave exactly as normal cells, although Krause and Plaut have suggested that the incorporation of thymidine- H^3 into cell nuclei may result in modification of the DNA molecule. The use of thymidine- H^3 is an excellent method for demonstrating zones of cellular proliferation and tracing the migration of labeled cells.

Despite the volume of reported work in the field of cell kinetics, few investigations have been concerned with cell populations in the respiratory

tract. Bertalanffy and Leblond, in a study of the rat lung using the technique of colchicine arrest and mitotic counting, described four types of cells in the alveolar tissues of the rat: (1) vacuolated alveolar cells, (2) non-vacuolated alveolar cells, (3) endothelium-like cells, and (4) blood cells. They concluded that continuous mitotic activity of the lung suggested a continuous renewal of the two types of alveolar cells, and that the time taken for renewal of vacuolated alveolar cells was approximately 29.4 days and the time for non-vacuolated alveolar cells approximately 8.1 days. They considered the alveolar tissues a dynamic environment offering physiologic conditions for renewal of the two cell types at somewhat different rates. These workers did not report any study of cell turnover in the tracheobronchial epithelium.

In 1962 Spencer and Shorter published the results of an investigation of the turnover of cells in the respiratory tract of young albino mice by radiolabeling with thymidine- H^3 and radioautography. They concluded that the turnover time for epithelial cells was 21 days in the large bronchi and seven to ten days in the small bronchi and respiratory bronchioles. They believed that in the alveoli the turnover time was approximately seven days for non-vacuolated cells and in excess of three weeks for vacuolated cells.

More recently Shorter and co-workers have studied the cells in the respiratory tract in albino mice by radiolabeling with thymidine- H^3 . Their findings suggested that two cell populations existed in the epithelia of the trachea and large bronchi, one with a turnover time of less than two days and the other with a time of five to seven days. They observed that the turnover time in the small bronchi was five to seven days. Also in the alveoli they noted the existence of two populations of alveolar macrophage cells with different turnover times, some (possibly the non-vacuolated

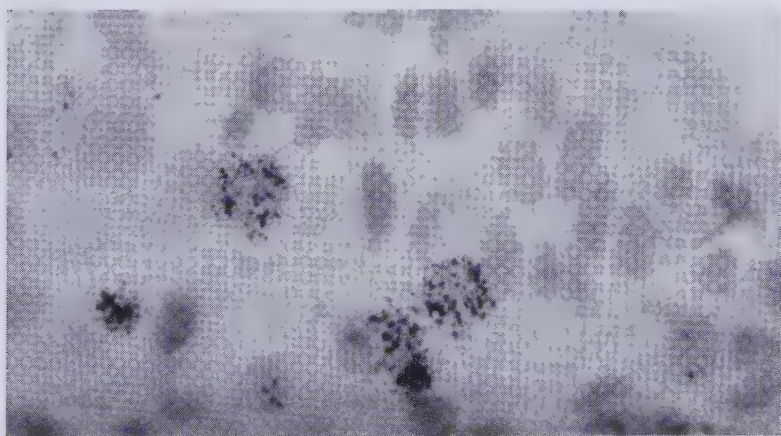


Figure 2. Labeling of nuclei in tracheal epithelium in mouse after parenteral injection of thymidine- H^3 . (Radioautograph: Kodak AR 10 stripping film. Hematoxylin and eosin; $\times 1500$.)

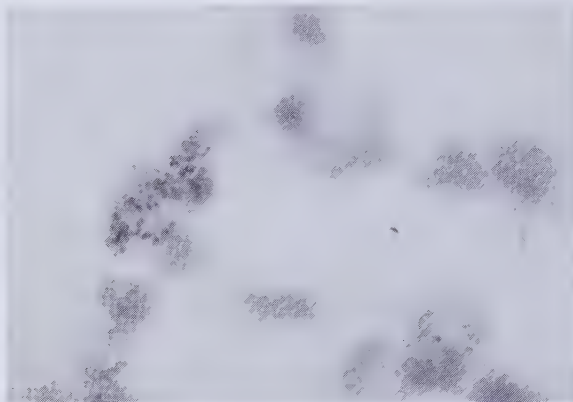


Figure 3. Labeling of nuclei of alveolar cells in lung of mouse six hours after parenteral injection of thymidine- H^3 . (Radioautograph: Kodak AR 10 stripping film. Hematoxylin and eosin; $\times 1500$.)

cells as classified morphologically by Bertalanffy and Leblond) having a turnover time of approximately seven days and the others (possibly the vacuolated cells described by those authors) a turnover time of approximately 35 days. Typical appearances of nuclear labeling seen in the radioautographs are shown in Figures 1, 2, and 3.

So far as we know, these are the main reports in the literature of studies of cellular proliferation in the respiratory tract to the present time. It is clear that many studies in this field are needed to increase our knowledge of the kinetics of cell populations in the respiratory tract in both physiological and pathological states. It is to be hoped that such studies will produce, ultimately, quantitative as well as qualitative information; but it is clear that many disciplines and much new research, involving the development of new techniques, will be required.

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The Pulmonary Alveolar Macrophage

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Only the last decade has brought a solution of the century-old controversy concerning the existence of a continuous epithelium lining the pulmonary alveolus. Studies of the lungs of rodents by electron microscopic techniques have confirmed the presence of such a lining,^{15, 18} and findings in human lungs have agreed with these observations.⁹ There appears to be little difference in the structure of alveolar tissue among various mammalian species, and generalizations may be made to hold for each.

The attenuated pulmonary-surface epithelium forms a continuous lining. Nuclei are not numerous and mitochondria are few. There are no demonstrable pores in the cell membranes and no spaces between the cells or in the basement membranes which would allow other cells or foreign material to pass to or from the interstitial tissue of the lung. The structure of the cytoplasm appears similar to that of the endothelium of the capillaries which underlie it and are separated from it by the basement membranes of each cell and the varying space between. In this relatively featureless cytoplasm, small vesicles are present and invaginations of the cell membranes resemble the changes of pinocytosis in other cells.

Within the alveolar space itself—and most often found resting on the attenuated cytoplasm of the lining cell—are the alveolar cells (Fig. 1). These correspond in general to the pulmonary macrophage or histiocyte and are representative of the reticuloendothelial system in the lung. Alveolar cells are actively phagocytic. They may be found in specimens of sputum and bronchial secretions as exfoliated elements from the terminal part of the airway, whether they have taken part in phagocytosis or not. Several of them may join together to form a foreign-body giant cell. Various morphologic forms of alveolar cell have been described, some resembling diffuse primitive cells like fibroblasts and other more circumscribed cells with or without numerous cytoplasmic vacuoles.³ They usually are mononuclear and have abundant cytoplasm containing many ribosomes and a well-defined endoplasmic reticulum. There is an abundance of

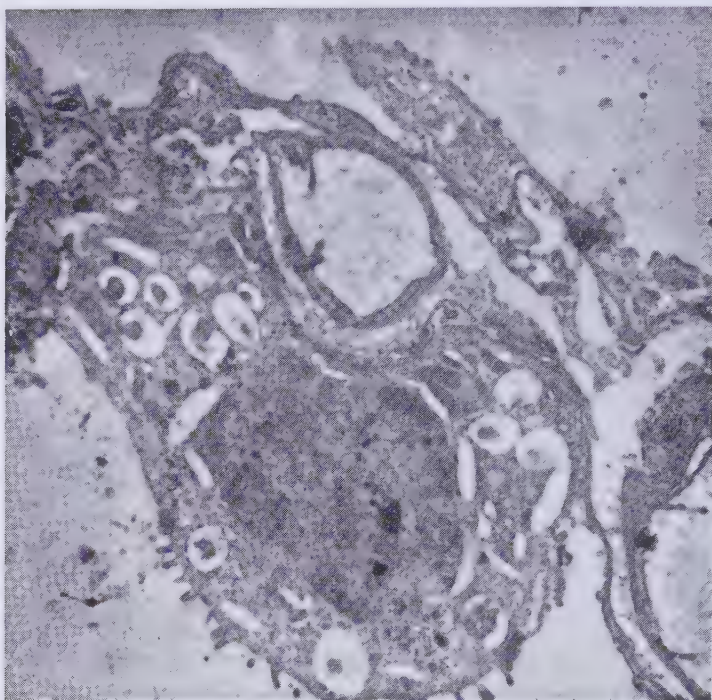


Figure 1. Alveolar cell with solitary nucleus and many vacuolated inclusions, resting on the alveolar lining ($\times 4000$). (From Divertie, M. B., and Brown, A. L., Jr.: The fine structure of the normal human alveolocapillary membrane: An electron microscopic study. *J.A.M.A.* 187: 938-941 [Mar. 21] 1964. By permission of the American Medical Association.)

organelles and inclusions, some of which are vacuolated. The well-developed endoplasmic reticulum and numerous ribosomes suggest active synthesis of protein.

In a recent study carried out on mouse lung, the findings suggested that two populations of alveolar cells may exist—one with a turnover time of approximately seven days and another with a turnover time of 35 days.²³ It was not possible in that study to differentiate histologically between vacuolated and non-vacuolated macrophages; but Bertalanffy and Leblond established life cycles of eight days for non-vacuolated and 29 days for vacuolated cells, and no doubt these two studies are in essential agreement.

In the normal lung the macrophages or dust cells rest on the alveolar lining cells and short microvilli protrude from their cytoplasm. The two layers are entirely distinct from each other; and although it has been suggested that alveolar cells might develop from lining cells,⁶ we were unable to find evidence for this in a recent study on human lung.⁹

Apart from the hypothesis of origin from the alveolar epithelium, it has been proposed that the macrophages may arise from the connective tissue,¹⁴ from capillary endothelium,¹¹ or from leukocytes.¹² Phagocytizing

leukocytes are not encountered commonly in the alveolar spaces, and their presence usually is associated with local irritation that could have caused their escape from the bloodstream. Since they may be seen to be phagocytized by the macrophages, they themselves evidently are foreign bodies within the alveoli.

Electron microscopic studies using thorium dioxide¹⁹ and India ink¹⁶ have confirmed the phagocytic properties of these cells. Phagocytosis occurs by a compound type of infolding of the plasma membrane, with formation and subdivision of vacuoles which subsequently move freely within the cytoplasm of the cell. Their limiting membranes have the triple-layered structure of the cell boundary. The inclusion bodies vary in their morphology and probably are products of phagocytosis with differences in appearance due to concentration, hydrolysis, or specific changes in chemical structure. The lamellations present in some are similar to lipid or lipoprotein structures such as are seen in the myelin sheath. Karrer¹⁶ has suggested that these lamellae appear secondarily in more homogeneous inclusions by an as yet undetermined process, perhaps a synthesis by the cell from ingested material.

In contrast to the active phagocytosis carried on by these macrophages, there is virtually no ingestion of foreign particles by the cells of the alveolar lining. It seems probable that light microscopy studies describing phagocytosis by the lining cells refer to macrophages resting on the alveolar epithelium and performing their function there. The absence of phagocytic activity supports Bremer's belief that the alveoli have a lining of entodermal origin. Since phagocytosis is generally a function of cells of mesodermal origin, it seems reasonable to assume that the alveolar macrophages belong in this category also. The differences in morphology and function between the two types of cell seem to indicate the likelihood of different physiologic properties also, and the evidence favors a connective-tissue origin for the macrophage.

In the tracheobronchial tree, the ciliary action of the epithelial lining ensures excretion of foreign particles which alight on its surface. Particles falling onto the alveolar surface are eliminated more slowly, and the mechanism by which this is accomplished remains a matter of debate. Large particles such as are found in asbestosis cannot be ingested by alveolar cells and remain in the alveoli to produce extensive fibrosis. Smaller particles are ingested by phagocytes; the fluid lining the alveolus may carry them to the phagocytes for ingestion.²⁰ The proliferation of phagocytes in response to such a stimulus increases the efficiency of this method of handling extraneous dust particles, and after ingestion the cell enlarges, becomes more rounded, and—most probably after detachment from the alveolar wall—disintegrates. It has been suggested that the released particles are then taken up by a succession of phagocytes, and by this intracellular and extracellular transport they reach the ciliated epithelium of the respiratory bronchioles and start their journey to expulsion

from the airway, or they pass into the lymphatics to gain the adjacent lymph nodes.¹³ The method by which this latter passage is accomplished is presently unknown.

Vigliani and associates have proposed that an unknown substance liberated from dead pulmonary macrophages may be a stimulus to the formation of collagen and they believe that this is the important factor in the production of silicosis. Although this idea remains purely speculative, it is interesting that filamentous structures have been demonstrated at high magnification in the cytoplasm of normal guinea-pig and rabbit peritoneal macrophages and in normal guinea-pig and human blood monocytes.⁸ These were believed to be physiologic constituents of the cells, and it was suggested that conceivably they might represent collagen precursors. Allgöwer and associates have shown that mononuclear blood cells may change into fibroblasts and form considerable amounts of hydroxyproline, a major constituent of collagen, thus lending some support to this unproved theory. Uncertainties inherent in the various methods of experiment still must be taken into account.

A comparison of the phagocytic and bactericidal abilities of macrophages from guinea-pig lung and mouse peritoneum showed both to be phagocytic, but the lung cells had relatively little bactericidal power.²² In spite of this the cellular acid phosphatase, which has been suggested as an index for reticuloendothelial activity, was higher in the alveolar macrophages than in the peritoneal. This characteristic probably is related to the site from which they were obtained. Neither this parameter nor the relatively increased oxygen consumption of the alveolar cells accounted for the apparent discrepancy in their efficiencies, even when allowance was made for species difference.

The alveoli of mammalian lung are coated by a thin film of lipoprotein which has the property of lowering the tension of the alveolar surface in order to maintain stability of the air spaces.²¹ It is deficient in the respiratory-distress syndrome of the newborn (hyaline-membrane disease), a condition attended by extensive atelectasis with deposition of fibrin in the fine air spaces.² It has also been found to be deficient in the atelectatic lungs of patients and animals following prolonged extracorporeal circulation using pump oxygenators. An extension of this observation has revealed that the lungs can be lethally disturbed by substances liberated in the circulation.²⁴ At the present time it appears that the pulmonary surfactant is a complex made up of at least eight components in fairly definite proportions. They may be grouped in three major categories, each with a specific function: unsaturated phospholipid, producing low tensions; nonphosphated lipid, protecting the phospholipid against oxidation; and protein, acting as a skeleton to hold the lipid body together.⁷ Klaus and his associates believe that the surfactant lining the alveolus develops during lamellar transformation of the mitochondria of the alveolar histiocytes. If this is so,

a great deal of investigation will be necessary to determine the function of the alveolar cell in these and other pathologic states.

While these cells proliferate in response to alveolar invasion by dust particles and are prominent in certain pneumoconioses, they also may proliferate in response to radiation damage and to various infections as well as to many other stimuli. The stimulus for their multiplication in pulmonary alveolar proteinosis has not been identified. In this disease they appear to be larger than normal and to undergo dissolution in considerable numbers in the alveolar spaces, which themselves are filled with an abnormal lipid material in which lamellated figures recently have been demonstrated.¹⁰ These figures suggest an origin from the alveolar cell itself.

CONCLUSION

In the advanced state of our present knowledge it is remarkable that the macrophage, so readily available in bronchial secretions, should be so poorly understood. It seems reasonable to expect that this deficiency will be repaired in the not too distant future, and a more precise appraisal made of the origin and functions of this alveolar cell.

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Pulmonary Surfactant

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Perhaps the most important development in pulmonary physiology during the past decade has been the elucidation of the role of a substance which occurs in the lining layer of the alveoli of the mammalian lung. This fluid layer is anatomically in contact with the gas in the alveoli and represents the first layer of the "alveolar-capillary membrane" through which oxygen diffuses in its passage from the external environment to the blood. The unique material it contains has been given several names (surface active substance, substance X, surface tension lowering substance, anti-atelectasis factor, and so on). For the sake of brevity it may be called "surfactant."

NATURE AND ORIGIN OF SURFACTANT

The precise chemical structure of surfactant has not yet been defined, but recent studies suggest that it is a lecithin-protein complex.^{13, 14, 27} Its presence in the normal human and other mammalian lung has been demonstrated consistently. However, it does not seem to be present in the lungs of other vertebrates.^{9, 21}

The presently available evidence indicates that surfactant is produced by alveolar epithelial cells. The earliest reference to the source of an "alveolar mucoid film" was by Macklin in 1954. He proposed that a specific type of alveolar epithelial cell, which he called the "granular pneumonocyte," secretes a film which functions to maintain a "constancy in the surface tension of the alveolar wall." Recent studies suggest that the mitochondria of the alveolar epithelial cells undergo transformations ("lamellar forms") which are associated with production of surfactant.^{5, 15, 16} In these studies a lack of normal surface activity in the mammalian lung has been observed when mitochondrial lamellar forms are absent (after vagotomy, and during fetal development). The evidence also suggests that strong surface activity is not present in the lung of animals whose alveolar lining cells do not show mitochondrial lamellar forms (toad, pigeon).

FUNCTION

The functional significance of surfactant can be appreciated only through an understanding of surface tension. Surface tension is the result of intermolecular attractive forces which are present in any liquid. At a gas-liquid interface the forces attracting an individual liquid molecule at the surface toward other molecules in the interior of the liquid are not balanced by similar forces attracting the molecule above the surface of the liquid. Thus there is a vector of force directed toward the interior of the liquid acting on the molecule. This results in a tendency of the liquid to contract to the smallest surface area per unit volume, and may be thought of as a tension developed at the surface of the liquid. Hence, one might say that the surface of any liquid behaves as if it were covered with an elastic membrane under tension, which acts in the plane of the surface. Since tension is measured as force per unit length, surface tension is conventionally expressed in dynes/cm.

Evidence that a fluid layer lines the alveoli of the mammalian lung has been available since 1926, when Terry reported experiments in which he obtained a clear protein-containing fluid through glass capillary tubes inserted into the alveoli of the cat. However, Terry's paper did not allude to the fact that wherever a liquid-gas interface is present, surface tension is acting.

In 1929 Von Neergaard became the first to postulate that surface tension is present in the terminal air spaces of the lung. To substantiate his hypothesis, he undertook a series of experiments to determine the relative contributions of tissue elasticity and surface tension to the retractive force of mammalian (including human) lungs. He reported that the elastic recoil of these lungs during stepwise deflation from large volume to small was considerably less (at comparable volumes) when they were filled with liquid than when they were filled with air. Filling the lungs with liquid abolished the air-liquid interface, and hence surface tension was no longer present. From these data he concluded that the greater retractive force of the air-containing lungs was due to surface tension. His data suggested that from two-thirds to three-fourths of the elastic recoil of the lung is due to surface tension, and that the remainder is due to tissue elastic forces. Similar studies during the past decade have corroborated and extended Von Neergaard's observations.^{3, 4, 20}

In 1955 Pattle²⁴ published observations on bubbles expressed from the parenchyma of excised lungs with his conclusion that their surface tension was very nearly zero as a result of their having a surface film of a lining substance which was secreted in the alveolar spaces and which constituted Macklin's mucous layer. If the actual surface forces in the intact lung were negligible, then how could this be reconciled with Von Neergaard's finding that surface tension contributes substantially to the elastic recoil of the lung?

The answer to this question was provided by the work of Clements and associates.⁶⁻⁸ They reasoned that perhaps lung surface tension was not constant but was large when lung volume and surface were larger and was small when volume and surface were small. This was supported by their finding that surface films could be obtained from saline extracts of lung tissue that had surface tension values of about 40 dynes/cm. when expanded but that decreased to less than 10 dynes/cm. when the area of the extract film was reduced and compressed. For comparison, surface tension of blood plasma is about 50 dynes/cm.

This ability of surfactant to reduce surface tension to very low values when the area of the film is reduced is a most important property, because it contributes to stability of the alveolar spaces, which otherwise might undergo collapse or overexpansion. The stability of alveolar spaces depends on the forces acting on their curved walls, the pulmonary alveoli having a more or less spherical shape.^{19, 22} A curved surface of a sphere under tension implies a pressure difference between the two sides of the surface, and for equilibrium the tendency of tension to contract the sphere must be exactly counterbalanced by the tendency of internal pressure to expand it. This is expressed in the Laplace relationship: $P = 2T/R$, where P is the expanding pressure, T is the tension in the wall, and R is the radius of the sphere.

Consider the situation of two adjacent alveoli of different diameter and radius. If T is the same for both alveoli, P will be larger for the alveolus with smaller R . Without other restraint, the greater pressure in the small alveolus will cause its air to flow into and expand the large alveolus while the small alveolus collapses. In regard to its internal surface the lung is like a foam with interconnected bubbles, which as suggested above would alone be very unstable, all the small spaces emptying eventually into one large space. Stability appears to be derived in part from the presence of tissue elements around the air spaces and by the exceptional surface properties of the lining layer. These are (1) that surface tension is low, thus permitting alveoli of small radius to be kept expanded by small distending pressures, and (2) that surface tension decreases as surface area decreases, which also tends to prevent small alveoli from collapsing as their radius decreases during exhalation.

RELATION TO DISEASE

After consideration of the function of surfactant in the lung, the clinical significance appears to be that atelectasis will result if, for any reason, surfactant is not present. During the past five years a considerable body of experimental evidence has accumulated correlating absence of normal surface activity with atelectasis. At the present time we may

enumerate the following clinical conditions in which atelectasis is associated with absence of normal surface activity in lung extracts: respiratory-distress syndrome of the newborn (hyaline-membrane disease); prematurity (in fetuses weighing less than 1200 gm.); atelectasis that sometimes follows cardiopulmonary bypass procedures; and compression atelectasis.

Gruenwald, and later Pattle,²⁵ suggested that surface tension might be important in atelectasis in the newborn infant. The most important contribution, however, was the study published by Avery and Mead in 1959. These investigators found a lack of normal surface activity in lung extracts from infants dying of respiratory-distress syndrome of the newborn, and from newborn infants weighing less than 1200 gm. This suggests that a lack of surfactant is of prime importance in the pathogenesis of atelectasis present in hyaline-membrane disease. The results obtained by Avery and Mead in respiratory-distress syndrome were confirmed by one of us (D.T.C.) in 1960.⁹

It appears that the clinical entity known as respiratory-distress syndrome of the newborn (formerly hyaline-membrane disease)²⁸ is a result of surfactant deficiency secondary to lack of synthesis by an immature cellular lining in the lung of these infants. Necropsy studies on infants with this clinical pattern indicate that the primary pathophysiologic event is atelectasis, and that the development of hyaline membrane and pulmonary hemorrhage follows.² There is evidence which indicates a simultaneous deficiency of fibrinolytic activity in the immature lung, to account for the development of hyaline membranes.¹⁷ However, it seems likely that death often occurs in infants with this clinical syndrome before hyaline membranes develop, in which circumstance the sole pulmonary abnormality is atelectasis. A recently published study demonstrates a correlation of mechanical properties of infant lungs with surface activity in extracts from them: more specifically, decreased surface activity correlates with increased instability of volume and tendency to collapse.¹²

In a series of surface-tension determinations performed on necropsy specimens in 1960-1961 by one of us (D.T.C.), it was found that the lungs of three of six patients who had expired within 48 hours of open-heart surgery with cardiopulmonary bypass had abnormal surface activity, suggesting a loss of surfactant.⁹ The method employed for determination of surface activity was similar to that described by Clements⁷ and by Avery and Mead, using saline extracts of 1-gm. lung specimens. Our data from a series of normal human lung extracts showed an average minimum surface tension of 5.8 dynes/cm. with a value of 2.3 for the standard deviation. When each of the lung extracts from patients having had cardiopulmonary bypass procedures was compressed to 17 per cent of its original surface area, the surface-tension minima (in dynes/cm.) were 22.1, 30.2, 23.0, 4.7, 5.2, and 8.0. These data suggest that cardiopulmonary bypass procedures in some way cause a loss of normal surface activity in

certain cases. In all six cases studied, some degree of pulmonary atelectasis was present; but abnormal (elevated) surface tension was found in only three.

While it may be postulated that surfactant deficiency in respiratory-distress syndrome of the newborn is due to lack of production because of immaturity, this cannot be true of the adult lung. Here it seems that the explanation for surfactant deficiency is related to the pulmonary blood flow. It has been shown in dogs that if one pulmonary artery is ligated, there is atelectasis and loss of surface activity in the ipsilateral lung, by the saline extraction method.¹⁰ In films prepared from lyophilized foam from the same lung, however, surfactant seems to be present, giving "normal" (very low) surface tension.³² To explain this finding, it has been postulated that interfering substances are present which prevent the surfactant from acting. Lecithin, lysolecithin, and polysorbate 80 (Tween 80) have been shown to do this;²⁶ and it is possible that a decomposition of surfactant occurs in the lung, yielding lysolecithin as a product to produce this interference with the remaining surfactant. In the process of lyophilization of the foam and subsequent preparation of the film, the surfactant-lysolecithin complex may be dissociated and the surfactant recovered, to produce normal surface activity in vitro. These circumstances may obtain where pulmonary-artery blood flow is stopped temporarily in cardiopulmonary bypass operations and in atelectasis produced by lung compression (another circumstance that recently has been found to produce abnormal surface tension in saline extracts of the lung).^{29, 30}

Heretofore, pulmonary atelectasis has been regarded as a phenomenon secondary to either bronchial obstruction or compression of the lung. With the recently developed knowledge of surfactant, a third cause of atelectasis must be considered: disorders producing surfactant deficiency.

SUMMARY

A unique fluid layer lines the terminal air sacs of the mammalian lung and contains material designated as surfactant because of its property of reducing surface tension to extremely low values when surface area is decreased. Current concepts of the nature and origin of surfactant are presented.

The physiologic role and functional significance of surfactant appear to reside in the prevention of mechanical instability and atelectasis in the lung. Experimental evidence relates surfactant deficiency to several pulmonary disease entities.

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Pulmonary Dysfunction After Open-Heart Surgery

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In the first year of open intracardiac surgery at the Mayo Clinic (1955), pulmonary complications were the commonest cause of mortality and excessive morbidity⁴ (Fig. 1). Since 1956, when certain precautions were instituted, clinically significant pulmonary complications have been infrequent. However, there is evidence from our own experience and that of others that some degree of pulmonary dysfunction still occurs after open intracardiac operations utilizing a pump-oxygenator. A review of the problem at this time thus appears warranted.

Clinical Features

The clinical features of pulmonary dysfunction can be related to the varying degrees of its severity (Table 1). Examples of mild degree continue

Table 1. *Clinical Features of Pulmonary Dysfunction Following Open-Heart Surgery*

Mild
Tachypnea
Normal or near-normal auscultatory findings
Normal evidence from chest roentgenogram
Moderate
Tachypnea
Slight use of accessory muscles of respiration (especially alae nasae)
Prolonged expiration with forced <i>end</i> -expiration
Mild cyanosis, or normal color
Normal or near-normal auscultatory findings
Normal or near-normal evidence from chest roentgenogram
Severe—as above, plus
Shallow breathing
Marked use of accessory muscles
Cyanosis
Numerous squeaky and coarse rales
Patchy or confluent areas of decreased radiolucency in chest roentgenogram

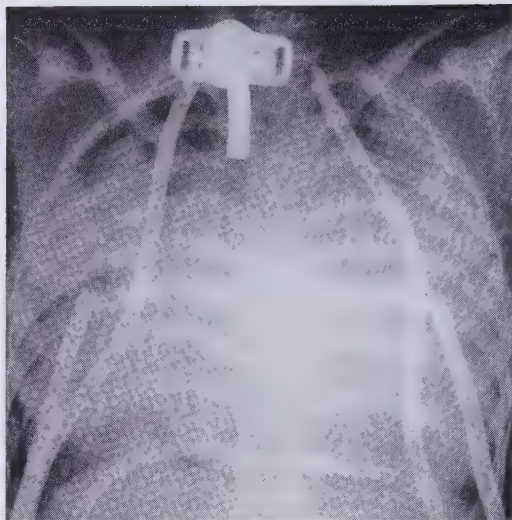


Figure 1. Chest roentgenogram made 24 hours after repair of ventricular septal defect with severe pulmonary artery hypertension August 23, 1955, showing extensive reduction of radiolucency in both lungs. Death occurred 12 hours later, at which time bilateral hemorrhagic pulmonary consolidation was observed.

to be frequent, but those of severe degree are now uncommon—fortunately, since this stage usually ends in death.

Ordinarily patients with mild or moderate degrees of pulmonary dysfunction improve spontaneously 48 to 72 hours after operation. Although cough is not a prominent symptom in the first few days after surgery, it sometimes appears as improvement occurs, occasionally with expectoration of loose, whitish, tracheobronchial secretions.

The clinical manifestations of this pulmonary dysfunction usually have disappeared by the fourth to the sixth postoperative day. A few patients, in the eighth to the twelfth postoperative days, develop fever, cough, dyspnea, and patchy areas of decreased radiolucency in the chest roentgenogram. This complication usually is self-limited, but at times the use of a broadly effective antibiotic seems helpful.

Pathology

Findings at necropsy after pulmonary dysfunction following open-heart surgery in man have indicated that alveolar collapse and intrapulmonary hemorrhage are dominant in the pathologic anatomy of this condition. Non-segmental alveolar collapse, first commented upon by Dodrill, has been prominent in our cases. Also, there is diapedesis of red blood cells into alveoli and in some instances engorgement of alveoli with blood. Perivascular hemorrhage and intense engorgement of small blood vessels in the lung occur. In experimental animals dying with this complication, Tomin and co-workers have observed large numbers of intravascular polymorphonuclear leukocytes in the lung. Deposits of hyaline membrane in alveolar ducts have been reported in some human cases.

Physiology

The commonest result of pulmonary dysfunction after open intra-

cardiac surgery is reduction of arterial pO_2 to less than the level seen in normal subjects breathing similar oxygen mixtures (Fig. 2). In our own experience, the oxygen saturation of hemoglobin in arterial blood usually can be kept at 95 per cent or more by the simple expedient of having the patient breathe oxygen-enriched air. In a few cases this does not suffice, and the oxygen saturation in arterial blood falls to dangerously low levels despite spontaneous breathing of such air. Since the arterial pCO_2 usually remains normal or near normal (Fig. 3), this derangement affects the exchange of oxygen more than it does the exchange of carbon dioxide.

Sometimes the minute volume of ventilation is abnormally high in these circumstances.⁷ The frequency of breathing is usually high, and tidal volume is often low. Mild reduction in diffusing capacity has been

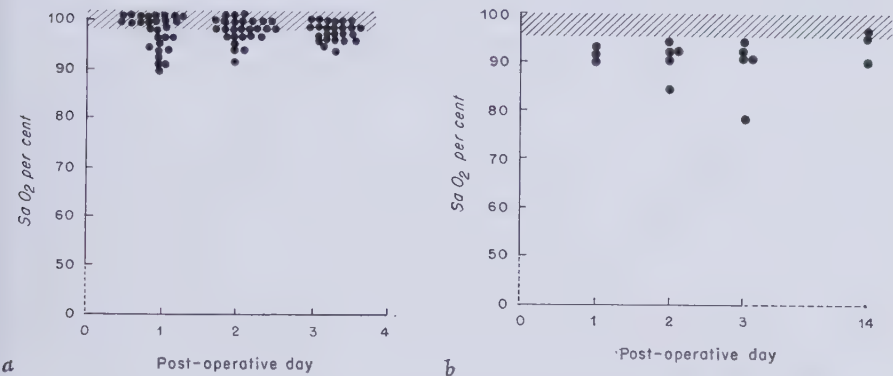
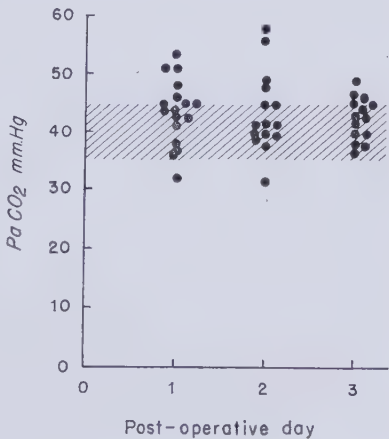


Figure 2. Oxygen saturation of arterial blood (SaO_2) following open intracardiac surgery of various types. Day 1 is the day of operation. Intracardiac right-to-left shunts were proved absent in each case by indicator-dilution curves recorded at radial artery after injection into right atrium. All patients were breathing spontaneously. *a*, Fractional concentration of oxygen in inspired air was about 0.4 (oxygen tent or face mask). *b*, Fractional concentration of oxygen in inspired air was about 0.2 (breathing air).

Figure 3. Arterial pCO_2 ($PaCO_2$) values after open intracardiac surgery of various types, in patients breathing spontaneously air enriched with oxygen to a fractional concentration of about 0.4 (oxygen tent or face mask).



reported,^{1, 5} although it is not clear that this differs significantly from that seen after other types of thoracic operations.

It is believed that the depression of arterial pO_2 is caused primarily by wide differences in ventilation-blood flow ratios in the lung, and by venous admixture resulting from perfusion of non-ventilated, airless alveoli.

Etiologic Factors

It is likely that even when open intracardiac surgery is done as perfectly as today's techniques allow, some degree of pulmonary dysfunction develops and persists for several weeks in nearly all patients. Recent work² has indicated that a reduction of surface-active agents in the lung occurs in experimental animals when blood flow through the pulmonary artery is interrupted, as it is during open intracardiac surgery. An increased tendency toward atelectasis results. Dr. Douglas T. Coles, in studying our own human material, has not found a consistent reduction of these agents in lungs after open intracardiac surgery. Yet, changes in surface-active agents in the lungs may be important etiologically in the postoperative pulmonary dysfunction of at least some patients. Patients are heparinized during open intracardiac surgery, and often have at least a mild bleeding tendency postoperatively. Minor trauma can initiate pulmonary or tracheal hemorrhage, which spreads rapidly under these circumstances. Tiny particles of fat³ and fibrin, usually present in the blood in varying degrees during whole-body perfusion from a pump-oxygenator, may lodge in pulmonary capillaries and contribute to postoperative pulmonary dysfunction. Aggregation of red blood cells has been observed during these procedures,⁶ and these aggregates too may lodge in pulmonary capillaries. There is a suggestion that patients have temporary widespread increase in capillary permeability after open intracardiac surgery, which implies that pulmonary edema can develop in them at lower pulmonary venous pressure than in normal individuals.

Patients who come to surgery with abnormal lungs may be more likely than others to develop significant pulmonary dysfunction postoperatively. For example, individuals with advanced degrees of disease at the mitral valve frequently demonstrate reduced compliance of the lungs and arterial desaturation. After surgery they more often than others require special measures directed at ventilation. The lungs of patients with tetralogy of Fallot or with severe pulmonary vascular disease usually have thin-walled, plexiform vascular channels. These individuals seem more likely to develop pulmonary hemorrhages after surgery than other patients.

The mechanical factors contributing to postoperative pulmonary dysfunction can only be surmised at this time. It has seemed that patients with previous thoracotomy have more pulmonary dysfunction after surgery than those without. It seems that if during open-heart surgery neither pleural space is opened, there is less pulmonary dysfunction than otherwise.

Postoperatively, pain probably contributes to the limitation of the tidal volume.

Certain things that normally should not occur during open-heart surgery can contribute to pulmonary dysfunction. Air passed into the pulmonary circulation during or after open cardiectomy can contribute to pulmonary edema. High levels of plasma hemoglobin, resulting from destruction of erythrocytes in the pump-oxygenator, have been reported to contribute to pulmonary derangement.⁹ Very high left atrial pressure during or after perfusion obviously can result in pulmonary edema. Reduction in the colloidal osmotic pressure of blood, from hemodilution by inordinate amounts of added glucose solutions, could be expected to predispose to pulmonary edema. Low cardiac output after operation contributes to arterial desaturation because the venous blood shunting through non-ventilated, airless alveoli has then an abnormally low oxygen content. Of course right-to-left shunting through residual intracardiac defects contributes to arterial desaturation.

Prevention

Additional knowledge of the subtle changes occurring in the blood and in the organisms during and after open intracardiac surgery is required to eliminate the problems of pulmonary dysfunction. Meantime, their incidence can be minimized by attention to all the factors known to contribute to this dysfunction.

Treatment

When the conduct of the operation is proper, most patients need only an oxygen-enriched atmosphere for the management of whatever pulmonary dysfunction is present. When the dysfunction is so severe that arterial desaturation is present, arterial $p\text{CO}_2$ is significantly elevated, or an inordinate amount of work is expended in breathing, tracheotomy and intermittent positive-pressure breathing are indicated. Such measures usually provide safe convalescence even in the face of significant pulmonary dysfunction.

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Congenital Vascular Malformations of the Lungs

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Congenital vascular malformations of the lungs, although relatively rare, are of interest to the physician because they may lead to significant disability that can often be alleviated by proper surgical management. It is not the purpose of this communication to deal in detail with every variety of pulmonary vascular anomaly that may occur but rather to present a classification of those commonly encountered clinically and to give a short discussion of each with illustrative case reports when indicated. Emphasis is placed on abnormalities affecting the main branches of the pulmonary vessels and their tributaries; thus such conditions as pulmonary stenosis, stenosis of the pulmonary veins, anomalies of the pulmonary trunk, and anomalous pulmonary venous connection when associated with major cardiac anomalies are not included. A classification of the lesions to be discussed is presented in Table 1.

Table 1. *Congenital Vascular Lesions of the Lung*

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- | |
|---|
| I. Abnormalities of the pulmonary circulation |
| A. Pulmonary arteries |
| 1. Agenesis of a pulmonary artery |
| 2. Stenosis of a branch or branches of the pulmonary arteries |
| 3. Pulmonary arteriovenous fistula |
| B. Pulmonary veins |
| 1. Abnormal pulmonary venous connection |
| 2. Varicosities of the pulmonary veins |
| II. Abnormalities of the systemic circulation |
| A. Arteries |
| 1. Intralobar pulmonary sequestration |
| B. Veins |
| 1. Azygos lobe |
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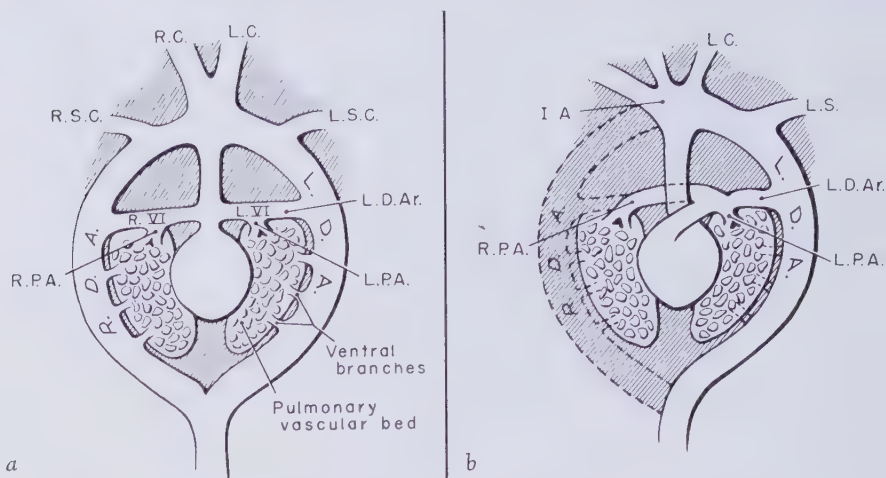


Figure 1. Schematic representation of development of pulmonary arterial circulation.

a, Early stage. Note connections between dorsal aorta and pulmonary capillary plexus.

b, At birth. Connections with aorta have been interrupted, and the entire blood supply to each lung is now by way of the pulmonary arteries derived from the proximal portions of the sixth arches.

R.VI and L.VI = right and left sixth arches

R.D.A. and L.D.A. = right and left dorsal aortas

R.P.A. and L.P.A. = right and left pulmonary arteries

R.S.C. and L.S.C. = right and left subclavian arteries

R.C. and L.C. = right and left carotid arteries

L.D.Ar. = left ductus arteriosus

I.A. = innominate artery

(From Sherrick, D. W., Kincaid, O. W., and DuShane, J. W.: Agenesis of a main branch of the pulmonary artery. *Am. J. Roentgenol.* 87: 917-928 [May] 1962.¹² By permission of Charles C Thomas, Publisher.)

EMBRYOLOGY

A brief summary of the available information regarding the development of the pulmonary vessels is a helpful introduction to a discussion of congenital vascular malformations of the lung.^{1, 4} The primordia of the lungs are derived from the foregut, and during the initial stages of development they share their blood supply with the foregut. It is only natural, then, that they should be supplied by visceral branches of the dorsal aorta. The pulmonary anlage is embraced by a capillary plexus, the so-called splanchnic plexus, which has connections with the dorsal aorta (Fig. 1, *a*). Normally the primitive pulmonary arteries, which develop as angioblastic buds from the region of the aortic sac, develop communications with this plexus, and the connections between the plexus and the dorsal aorta then atrophy (Fig. 1, *b*). A few of these connections persist in the form of bronchial arteries. A fault at this stage of development might lead to a persistence of connections between lung and aorta.

The pulmonary, or sixth, aortic arch plays a temporary but important role in the developmental aspects of pulmonary vascular anomalies, for while the pulmonary arch is connected temporarily during developmental life with the primitive pulmonary arteries, as they grow caudad from the aortic sac to the lung buds, it loses connection with the dorsal aorta except for that portion on the left which remains as a ductus arteriosus. An exaggeration of the process by which the distal segment of the sixth aortic arch disappears may result in obliteration of the proximal segment as well, leading to absence of the right pulmonary artery.

Pulmonary and bronchial veins are likewise the eventual persisting form of the original plexus of capillaries encompassing the primitive foregut and its lung bud. This plexus has numerous capillary anastomoses with two venous drainage systems: one, the cardinal system of veins from which such structures as the superior vena cava, the azygos vein, and the coronary sinus develop; the other, the umbilicovitelline system represented in its final stages of development primarily by the portal system (Fig. 2). During the early stages there is no direct communication between the venous supply of the lungs on the one hand and the heart on the other. During the next important developmental stage the channel from the sinoatrial region of the heart grows toward the developing lungs and eventually establishes communication with the pulmonary-venous bed. This channel has been called "the common pulmonary vein." Thereafter, the more primitive connections between the pulmonary-venous system and the cardinal and umbilicovitelline veins disappear, leaving the definitive normal condition in which all the pulmonary-venous system has direct connection

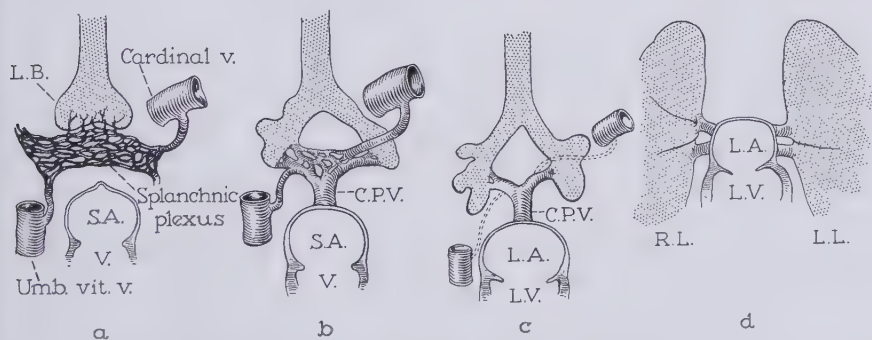


Figure 2. Stages in development of pulmonary veins.

a, Initially, the splanchnic plexus communicates with the cardinal veins and with the umbilicovitelline veins.

b, Later an outpouching (C.P.V.) of the sinoatrial region of the heart (S.A.) makes a secondary connection with the splanchnic plexus.

c, Next the previously existing connecting veins disappear.

d, The common pulmonary vein is ultimately incorporated into the left atrium (L.A.).

(Reproduced with permission from Edwards, J. E.: Pathologic and developmental considerations in anomalous pulmonary venous connection. *Proc. Staff Meet., Mayo Clin.* 28: 441-452 [Aug. 26] 1953).⁴

with the common pulmonary vein, which eventually becomes incorporated into the left atrium and disappears as an identifiable structure. Deviations from this normal pattern are represented mainly by retention of primitive stages wherein some of the primitive connections between the pulmonary-venous system and the cardinal or umbilicovitelline veins persist.

ABNORMALITIES OF THE PULMONARY CIRCULATION

Congenital Absence of a Branch of the Pulmonary Artery

The pulmonary vascular bed develops independently of the primary pulmonary arteries which are derived from the sixth aortic arches. Because of this embryonic development of the lung, it is possible for the various components to form in the absence of the ipsilateral pulmonary artery. More than 60 cases of such an anomaly have been reported. The affected lung is smaller in volume, and its ventilation is reduced, which, along with the appearance of enlarged bronchial arteries on this side, allows suspicion of the proper diagnosis from the roentgenogram of the thorax.

Agenesis of the pulmonary artery has been reported with equal frequency on the right and the left, although in the absence of associated intracardiac anomalies it has been more frequent on the right.¹² In nearly half of the cases, an anomalous systemic artery arising from the aortic arch or one of its branches, has supplied the involved lung, and in the remaining cases collateral circulation developing from the bronchial arteries has supplied blood to the lung.

Persons with this anomaly may be asymptomatic or may note recurrent respiratory infections, dyspnea on exertion, or hemoptysis. Once the abnormal chest roentgenogram has attracted attention to the condition, its diagnosis can be established by angiocardiology. The pulmonary artery on the involved side will not fill during the phase of flow of contrast medium through the pulmonary artery, and the contrast material will enter the involved lung only from the aorta via an anomalous systemic artery or the collateral bronchial artery. Best delineation is possible with injection of contrast material into the right ventricle or main pulmonary artery. No specific treatment for this anomaly is known.

CASE 1 (Case Included in a Previously Reported Series¹²). The patient, a 58-year-old man, had had pneumonia as a child. (This patient was older than any other with this anomaly whose case has been reported.) Recently the patient had begun to have angina pectoris. He had been known to have hypertension for 30 years. Mild cyanosis of the nails was observed, but he had no respiratory symptoms of note. The chest roentgenogram had shown decreased volume of the left lung, a right aortic arch, and rib notching on the left (Fig. 3, *a*). The last named finding, along with thickening of the pleura, suggested that much of the blood supply to the left lung was through the pleural collateral circulation arising from the intercostal arteries. The angiocardiology (Fig. 3, *b*) demonstrated complete absence of filling of the left pulmonary artery. No treatment was recommended for this condition.

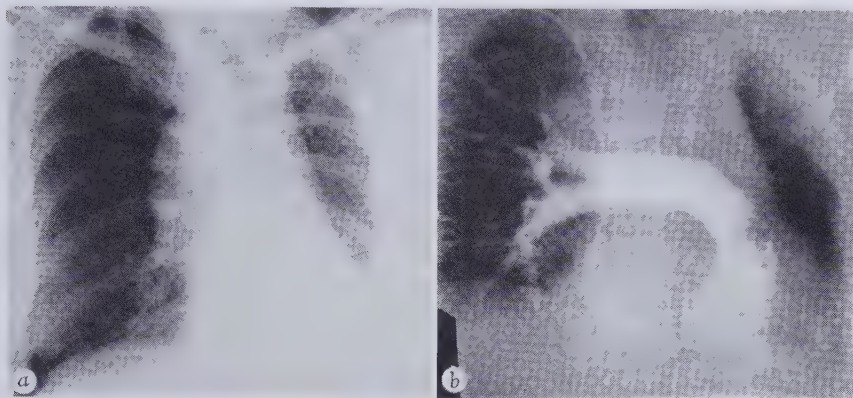


Figure 3 (Case 1). Absence of the left pulmonary artery.

a, Posteroanterior thoracic roentgenogram showing decrease in volume of left hemithorax with shift of mediastinum to left and slight elevation of left hemidiaphragm.

b, Angiogram with injection into the right ventricle shows agenesis of the left main branch of the pulmonary artery.

(From Sherrick, D. W., Kincaid, O. W., and DuShane, J. W.: Agenesis of a main branch of the pulmonary artery. *Am. J. Roentgenol.* 87: 917-928 [May] 1962.¹² By permission of Charles C Thomas, Publisher.)

Stenosis of the Branches of the Pulmonary Artery

Stenosis of the branches of the pulmonary arteries occurs in two principal forms: (1) a single site of stenosis near the origin of either the right or left pulmonary artery, but probably more commonly on the right, and (2) multiple, and usually bilateral, stenoses of segments of the pulmonary arteries and their lobar and segmental branches, typically with corresponding multiple poststenotic dilatations. Both types are commonly, but not necessarily, associated with intracardiac anomalies of various kinds. The first type causes a systolic murmur but no significant pulmonary hypertension or symptoms, whereas multiple bilateral stenoses may cause severe pulmonary hypertension, a continuous murmur, and presumably right ventricular failure, although the natural history of the condition is unknown.

The diagnosis must be established by cardiac catheterization and angiography, and especially by injection of contrast medium into the right ventricle. If severe pulmonary hypertension exists, and especially if symptoms or signs of cardiac origin are present, surgical intervention may be considered. An operation performed for this condition has been described in another paper of this issue;⁹ the evidence is suggestive of a beneficial result.

CASE 2. A 6 $\frac{3}{4}$ -year-old boy was referred because of chest pain of a month's duration. Cyanosis of the mouth and fingers had been noted with crying and exertion since birth but had decreased gradually in recent years. Physical examination revealed diminished femoral pulses. A systolic thrill and a grade 4 systolic murmur over the upper part of the sternum that was transmitted into the neck and back

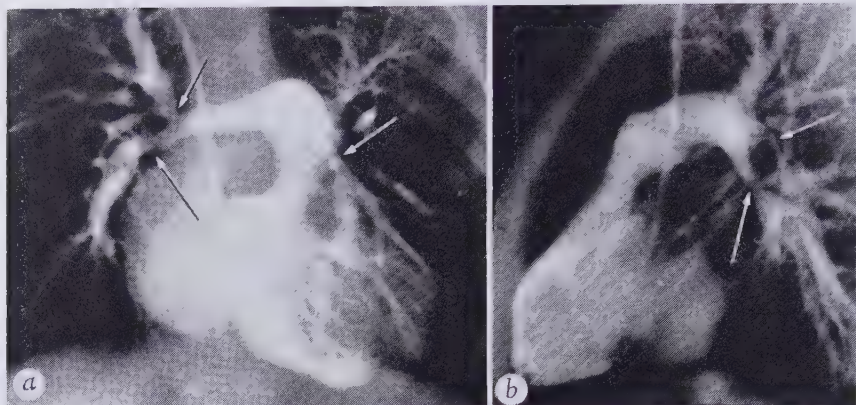


Figure 4 (Case 2). Angiocardiogram showing stenosis of multiple branches of the pulmonary arteries (arrows). *a*, Posteroanterior view. *b*, Lateral view.

were noted. The thoracic roentgenogram showed normal conditions. Cardiac catheterization and angiocardiography confirmed the clinical impression of coarctation of the aorta. Multiple bilateral stenoses of branches of the pulmonary artery were demonstrated (Fig. 4). Right ventricular pressure was 72 mm. of mercury systolic. Operation was not advised because of the lack of symptoms, although operation for repair of the coarctation and perhaps of the stenosis of the left pulmonary artery is planned at age 8.

Pulmonary Arteriovenous Fistula

A pulmonary arteriovenous fistula is a vascular malformation of the pulmonary vessels in which there is persistence of one or more communications between branches of the pulmonary artery and vein which bypass the pulmonary capillary bed. Pulmonary arteriovenous fistulas may be single or multiple; in about half of the cases they are associated with capillary abnormalities in other parts of the body as part of the syndrome known as hereditary telangiectasia or "Rendu-Osler-Weber disease."⁸ It has been postulated that telangiectasia is commonly associated with a pulmonary arteriovenous fistula because of action of 5-hydroxytryptamine (serotonin) on the systemic circulation as the lungs could not detoxify any serotonin that passed through the fistula and not through the pulmonary capillary bed.¹⁴ The etiology of pulmonary arteriovenous fistula is uncertain, although it must be related in some way to the persistence of vessels in the primitive splanchnic capillary bed.

As a result of this abnormal communication, there is, in effect, a right-to-left shunt with desaturated blood from the pulmonary artery reaching the left atrium directly through a pulmonary vein without becoming oxygenated. If this right-to-left shunt is in the neighborhood of 25 to 30 per cent, classic clinical findings of the disease may be present, namely cyanosis, polycythemia, and clubbing of the fingers. A bruit can often be heard and a thrill palpated in the vicinity of the lesion if it is

sufficiently large. The usual roentgenographic pattern is that of a rounded or oval shadow in the parenchyma of the lung, and it may appear to be connected to the pulmonary hilum by vessels which can be more easily identified by the use of tomography.⁷ Angiocardiography is the most definitive diagnostic technique and may disclose multiple arteriovenous communications not suspected clinically.

When symptomatic arteriovenous fistulas are untreated, a variety of complications may occur including bacterial endocarditis or endarteritis with abscess formation, rupture of the fistula with bleeding, or central nervous system symptoms secondary to embolism or brain abscess. Surgical excision is the only effective treatment, as all medical measures have proved without benefit. It is clearly indicated in symptomatic patients, and an effort should be made in resecting the lesion to preserve as much pulmonary tissue as possible. Perhaps not all lesions require surgical treatment, and we have been reluctant to advise resection for the asymptomatic, small lesion. In the presence of multiple lesions, excision of the major one seems justified in the hope of converting a cyanotic patient to an acyanotic one. An example of one such patient is presented briefly.

CASE 3. A 39-year-old woman with a five-year history of clubbing of the fingers and toes had experienced a recent episode of rapid heart action and dyspnea. Slight cyanosis was apparent on physical examination, and hemangiomas were present on the back of the tongue and on the lips. A systolic bruit was audible over the left intrascapular region. The hemoglobin level was 16.6 gm. per 100 ml. The thoracic roentgenogram demonstrated an irregular lesion posteriorly on the left and a small nodular lesion in the right pulmonary field. Angiocardiography revealed multiple pulmonary arteriovenous fistulas, four on the left and one on the right (Fig. 5, *a* and *b*). The large one on the left was successfully removed by segmental resection, and the three other fistulas on the left were removed by wedge excision.* The patient made an uneventful recovery.

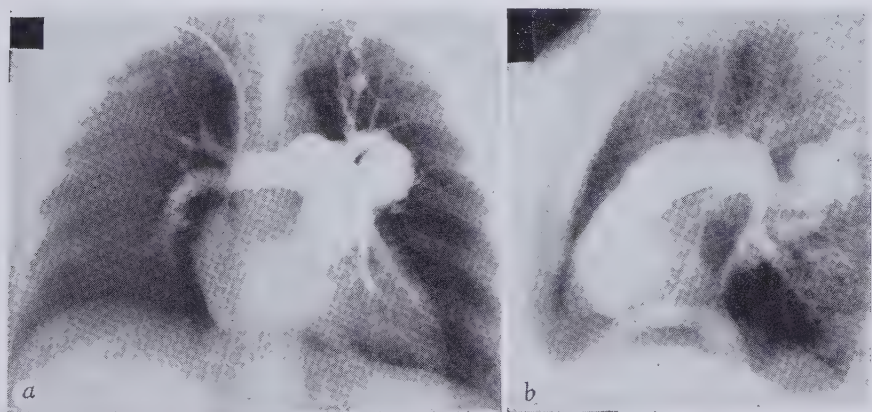


Figure 5 (Case 3). Multiple pulmonary arteriovenous fistulas. Selective angiograms. *a*, Posteroanterior view. *b*, Lateral view.

* We are grateful to Dr. W. S. Payne for permission to report this case.

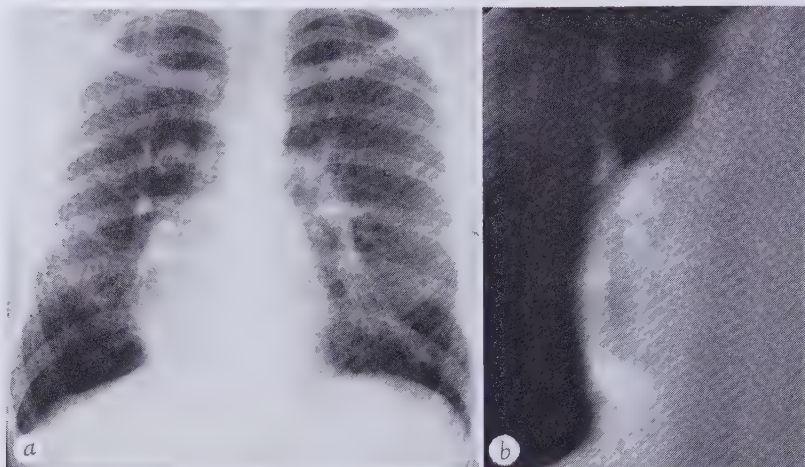


Figure 6 (Case 4). Anomalous connection of right pulmonary veins to inferior vena cava. *a*, Posteroanterior thoracic roentgenogram. *b*, Tomogram.

Abnormal Pulmonary Venous Connection

Although most instances of abnormal pulmonary venous connection are a part of a major cardiac malformation, anomalous pulmonary venous drainage of the right lung into the inferior vena cava may be an isolated condition. This condition represents a persistent venous communication between the pulmonary capillary bed and the caval system. Such associated abnormalities as dextroposition of the heart and hypoplasia or agenesis of a portion of the right lung or of the arterial vessels supplying the right lower lobe may coexist. Occasionally the abnormal pulmonary vessel may connect with the superior vena cava. Connection with the inferior vena cava is more common, and the characteristic roentgenographic appearance has led to the term "scimitar syndrome."¹⁰

The essential hemodynamic abnormality is a left-to-right shunt, and although the majority of patients are asymptomatic, the condition may result in the symptoms of easy fatigability and dyspnea.⁵ Thoracic roentgenograms may be helpful in making the diagnosis (Fig. 6, *a*). The right lung often appears hypoplastic, and there may be asymmetry of the thorax with dextroposition of the heart. Occasionally the abnormal vessel can be recognized on the plain posteroanterior roentgenogram as a crescentic saber-shaped shadow of vascular density running downward parallel to, or behind the right side of, the heart and disappearing below the diaphragm.³ Tomograms may be helpful in visualizing this abnormal vein (Fig. 6, *b*) although angiocardiography is required for a definitive diagnosis.

Even in the absence of symptoms, it seems reasonable to consider patients with this disease in whom a large shunt has been demonstrated as having essentially the same prognosis in regard to hemodynamic changes as patients with atrial septal defect. Thus, operation should be considered

in order to prevent heart failure or pulmonary vascular changes as a result of the large pulmonary flow.

CASE 4. A 20-year-old man, known to have had a heart murmur for 12 years, gave a history of easy fatigue of many years' duration. Physical examination revealed a grade 2 midsystolic presternal murmur. Thoracic roentgenograms showed increased pulmonary vascularity on the left with dextroposition of the heart (Fig. 6, *a*). A large vessel that could be seen paralleling the right border of the heart was seen more clearly by tomography (Fig. 6, *b*). Cardiac catheterization demonstrated normal pressures with a 50 per cent left-to-right shunt resulting from an abnormal connection of the veins draining the right lung to the inferior vena cava. Successful correction of the defect was accomplished while employing extracorporeal circulation.*

Varicosities of the Pulmonary Veins

Varicose malformation of the pulmonary veins is an extremely rare lesion which seldom gives rise to symptoms. It is detected, as a rule, by the abnormal appearance of the thoracic roentgenogram. The lesions appear as rounded shadows in the lung or, more rarely, are visualized as an elongated or fusiform shadow. Selective angiocardiology is useful in making a definitive diagnosis, and such a case has recently been reported from this institution and is summarized here.¹⁵

CASE 5. A 7-year-old girl was seen at the Mayo Clinic for evaluation of congenital heart disease. A thoracic roentgenogram revealed several rounded shadows in the midportion of the right lung suggestive of pulmonary arteriovenous fistulas (Fig. 7, *a*); these were more clearly identified by tomography (Fig. 7, *b*). Selective angiocardiology demonstrated gross abnormality of the pulmonary veins in the right lung (Fig. 7, *c*). A large, dilated, tortuous superior pulmonary vein appeared to drain the entire right upper lobe and the superior segment of the right lower lobe. Pulmonary veins in the left lung were normal.

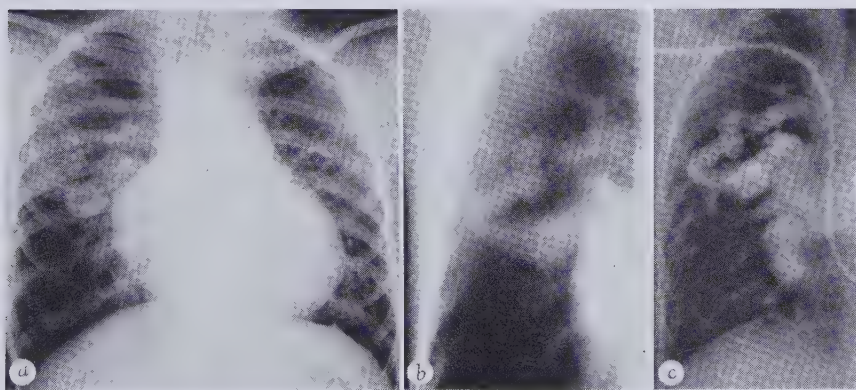


Figure 7 (Case 5). Varicosity of the pulmonary veins. *a*, Posteroanterior roentgenogram. *b*, Tomogram. *c*, Angiogram. (From Vengsarkar, A. S., Kincaid, O. W., and Weidman, W. H.: Selective angiocardiology in diagnosis of varicosity of the pulmonary veins: Report of a case. *Am. Heart J.* 66: 396-398 [Sept.] 1963.¹⁵ By permission of the publishers, C. V. Mosby Company.)

* We are grateful to Dr. J. W. Kirklin for permission to report this case.

ABNORMALITIES OF THE SYSTEMIC CIRCULATION

Arteries: Intralobar Pulmonary Sequestration

A congenital pulmonary malformation in which a portion of an otherwise normal lobe has no normal connection with the bronchial tree or the pulmonary arterial circulation, receiving rather its arterial supply directly from the aorta by one or more anomalous branches, is known as "intralobar pulmonary sequestration." Controversy exists regarding the exact cause of this malformation. The opinion has been advanced on the one hand that the lesion is the result of compression and sequestering of a segment of the lung by persistence of a vascular connection between the lung and the aorta.¹¹ By the same token, it has been proposed that the defect is primarily a pulmonary one with abnormal development of a portion of the lobe, which, lacking normal pulmonary circulation, retains the primitive connection between the capillary bed and the aorta.¹³ It is unlikely that the abnormal systemic vessel represents a dilated bronchial artery in response to infection as has been suggested.⁶

Pathologically, the involved portion of the lung may exhibit one or more cystic areas, or it may consist of a nonaerated mass of pulmonary tissue traversed by dilated bronchi. The abnormal vascular connection with the aorta may be single or multiple, usually the former, with the vessel either coming off directly from the thoracic aorta or from the abdominal aorta below the diaphragm. The vessel usually enters the lung through the pulmonary ligament. The lesion is usually located in the basilar segments of the lower lobes, particularly in the posterior segments. Rarely such a lesion has been described in the upper lobes.¹⁶ The "sequestered" portion of the lung may reestablish communication with the bronchial tree.

The patient with pulmonary sequestration may be asymptomatic unless such a communication with the bronchial tree develops, in which case a cough, purulent sputum, fever, and even frank bronchopneumonia may be observed. Thoracic roentgenograms demonstrate a round, oval, or lobulated shadow in the posterobasal segments of the lung, more often the left than the right. In the presence of a communication between the diseased lung and the bronchial tree, an air-fluid level may be demonstrated. The aberrant systemic vessel may occasionally be seen on the plain posterolateral thoracic roentgenogram, but tomograms may be required for its delineation. It is most readily demonstrated by retrograde thoracic aortography.

Surgical resection is the proper treatment and can usually be accomplished by segmental resection of the basilar segments of the involved lobe. Care must be exercised to avoid inadvertent injury to the anomalous vessel, for if severed, it may retract to an inaccessible position.

CASE 6. A 20-year-old railway clerk was referred with a two-month history of chills, fever, malaise, and increasing cough productive of greenish-yellow sputum.

Physical examination gave negative results. Thoracic roentgenograms revealed a shadow at the base of the right lung posteriorly (Fig. 8, *a* and *b*). Retrograde thoracic aortography demonstrated an anomalous vessel arising from the aorta and supplying the diseased area (Fig. 8, *c*) which when excised proved to be an epithelial-lined cyst associated with a systemic artery (Fig. 8, *d*).

Veins: Azygos Lobe

A common anomaly of the systemic venous system that involves the lung secondarily is the azygos lobe. It is seen in 0.5 to 1 per cent of routine thoracic roentgenograms,² and its cause is unknown. In this condition the azygos vein comes to lie within the substance of a portion of the upper lobe, and the anomalous part is separated from the remainder by a double fold of visceral pleura which is carried down with the azygos vein. The

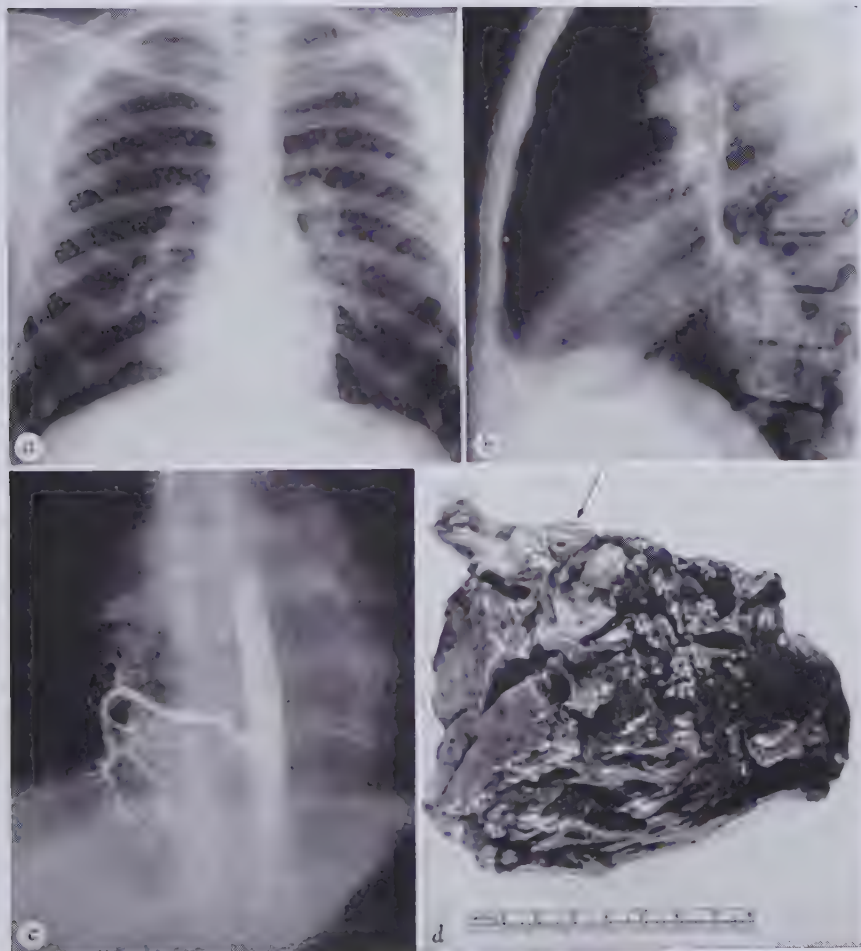


Figure 8 (Case 6). Intralobar pulmonary sequestration. *a* and *b*, Posteroanterior and lateral thoracic roentgenograms. *c*, Thoracic aortogram. *d*, Surgical specimen (arrow indicates cyst). Anomalous vessel not seen. See text for details.

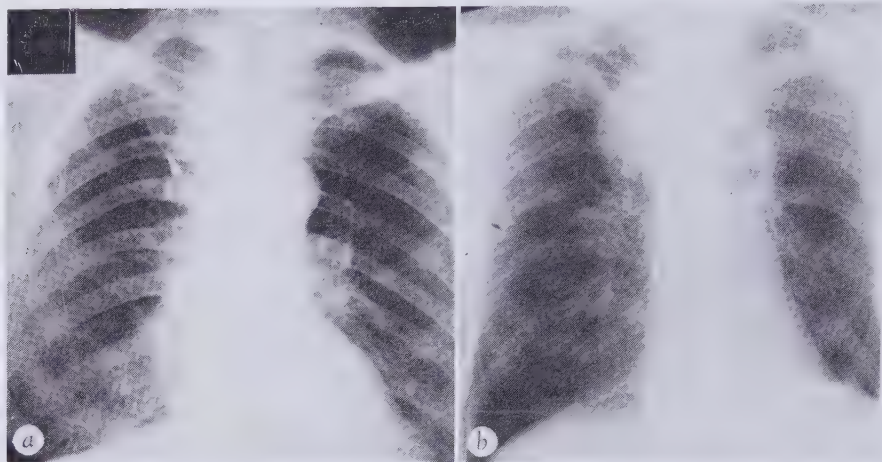


Figure 9. *a*, Azygos lobe demonstrated on routine posteroanterior thoracic roentgenogram. *b* (Case 7), Carcinoma arising in an azygos lobe.

mechanism of this malformation is responsible for the characteristic "inverted comma" seen on the thoracic roentgenogram (Fig. 9, *a*). The azygos lobe may be the site of tuberculous or neoplastic processes, and an example of the latter is recorded below.

CASE 7. A 62-year-old man was seen because of fatigue, loss of weight, cough, chills, and fever. A left upper lobectomy had been done a year previously for tuberculosis. Physical examination gave negative results. A thoracic roentgenogram showed evidence of an ovoid mass in the right upper lobe of the lung (Fig. 9, *b*). Exploratory thoracotomy revealed an inoperable carcinoma arising in an azygos lobe. Biopsy revealed grade 4 adenocarcinoma.

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Stenosis of Branches of the Pulmonary Artery: Surgical Repair

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Stenosis of the branches of the pulmonary artery has gained increasing attention in the past decade. With the widespread use of cardiac catheterization and angiocardiology, many cases of stenosis of the pulmonary artery and its branches have been recognized.^{1, 2, 4-8, 10-16, 18} The degree of stenosis has varied from minor to severe and the sites from single to multiple. In several cases congenital deformities of the heart or great vessels have not been associated. This condition was recognized and reported by Oppenheimer in 1938. Her case was unusual in that calcification was present in the branches of the pulmonary artery at the sites of stenosis, as well as in the aortic arch, in a patient who was only 17 months of age at death.

Since pulmonary valvular stenosis and stenosis of the main pulmonary artery are conditions better included with cardiac, rather than pulmonary, congenital anomalies, the present discussion shall be confined to stenosis of the branches of the pulmonary artery without any associated cardiac anomalies. This condition, however, can be, and most often is, associated with cardiac anomalies such as pulmonary stenosis, ventricular septal defect, atrial septal defect, and patent ductus arteriosus.

Cases of stenosis of the branches of the pulmonary arteries are divisible into two groups: (1) those in which isolated narrowing of either the right or left pulmonary artery is present, and (2) those in which stenosis occurs in multiple sites, usually bilaterally, not only in the primary pulmonary arteries but also in their lobar and segmental branches.

When a single site of stenosis is present, it is likely to be located at the origin of the right pulmonary artery and usually does not impose a significant hemodynamic burden. Luan and associates reported 10 such cases from their clinical experience. They adapted the theory of Madoff and co-workers, which explains the more frequent congenital absence of the right than the left pulmonary artery when unassociated with intra-

cardiac lesions, to account for the preponderance of stenosis of the right pulmonary artery. This hypothesis is based on the fact that the distal segment of the embryonic right sixth aortic arch, which extends posteriorly from the site of attachment of the right primitive pulmonary artery, disappears. If this degeneration should extend too far proximally or should result in angulation at the junction of the primitive pulmonary artery, stenosis could result. On the left, this segment does not disappear but becomes the ductus arteriosus, and presumably the hazard of stenosis at the origin of the left pulmonary artery is thus less. On the other hand, stenosis of the left pulmonary artery, when it does occur, has been attributed to abnormal constriction related to closure of the ductus after birth,^{7, 15} an adaptation of the so-called skodaic theory of coarctation.

The single site of stenosis results in a systolic murmur heard over the base of the heart, but since any diastolic gradient across a stenosis of this type is very small, a diastolic or continuous murmur is not present. Right ventricular pressures are not elevated in this condition in the absence of other cardiac anomalies. Hence, surgical correction is probably not indicated, nor has it been reported.

When stenosis is bilateral and multiple areas are present in the branches of the pulmonary artery, the hemodynamic burden imposed may be severe, since there may be no remaining unobstructed pathways for pulmonary blood flow. The multiple nature of this lesion suggests that it results from anomalous development of the pulmonary arterial tree from the pre-existing pulmonary vascular plexus.¹ Characteristically there is right ventricular and pulmonary arterial hypertension, even when unassociated with intracardiac anomalies, with resulting hypertrophy of the right ventricle as evidenced by the chest roentgenogram and electrocardiogram. The gradient persists into diastole across the stenoses in the cases of more severe stenosis and results in continuous murmurs which are usually widely transmitted over the entire thorax.

The diagnosis must be established by cardiac catheterization and angiocardiography, preferably by injection of contrast medium into the right ventricle. Agustsson and associates pointed out the characteristic pressure curve of the main pulmonary artery in which the systolic contour is identical to that in the right ventricle, with a steep descending limb and low diastolic plateau, which is related to the wide pulse pressure in the main pulmonary artery.

The few reports in the literature of this condition do not allow any conclusions with regard to long-term prognosis. It must be assumed that failure of the right ventricle is a serious hazard in the severe forms of the lesion. Although surgical correction of stenosis of the main pulmonary artery at the origin of the right pulmonary artery³ and at the origin of the left pulmonary artery has been reported,^{13, 14, 18} the case report that follows is believed to be the first report of an attempt to relieve multiple peripheral areas of stenosis in the branches of the pulmonary artery.

Reference was made to a similar operation, performed bilaterally in stages, by Smith* in a discussion following the recent presentation of Weinberg et al.

REPORT OF CASE

A 9-year-old boy was examined in June, 1962, because of a murmur audible since birth. He had always been active and asymptomatic until 6 months previously, when mild shortness of breath on exertion and abnormal fatigue at the end of the day became evident. On examination, there were no thrills, but a harsh systolic murmur of grade 4 (on the basis of 1 to 6), extending far into diastole, was audible over the upper part of the sternum and was well transmitted to the axillae. The electrocardiogram showed right ventricular hypertrophy which suggested systemic pressure in the right ventricle. The only abnormality on the chest roentgenogram was slight enlargement of the pulmonary artery and slight upturning of the apex of the heart.

These findings suggested the presence of pulmonary stenosis. Cardiac catheterization demonstrated no shunts either from blood oxygen saturation data or dye curves. The various pertinent pressure measurements are recorded in Table 1, and a representative frame from the angiocardigram is shown in Figure 1.

At operation on June 21, 1963, right anterolateral thoracotomy was carried out in the bed of the fifth rib, but the rib was not resected. A prominent systolic thrill could be felt over most of the lung. The anatomy of the right pulmonary artery and its hilar branches corresponded exactly to the findings on the pulmonary arteriogram, there being stenosis at the orifices of the apical and anterior segmental branches and at the origin of the right upper lobe branch itself, stenosis of the posterior segmental orifice, and mild stenosis of the intermediate artery just beyond the origin of the posterior segmental branch. Pressure measurements were as recorded in Table 1. Full equipment for cardiopulmonary bypass was available but was not employed. After the various arterial branches were clamped appropriately, a longitudinal incision was made from the right pulmonary artery along the stenotic right upper lobe branch into the poststenotic dilatation of its two divisions. An oval graft of azygos vein was sutured into this incision with the widest diameter of the graft corresponding to the narrowest portion of the artery (Fig. 2).

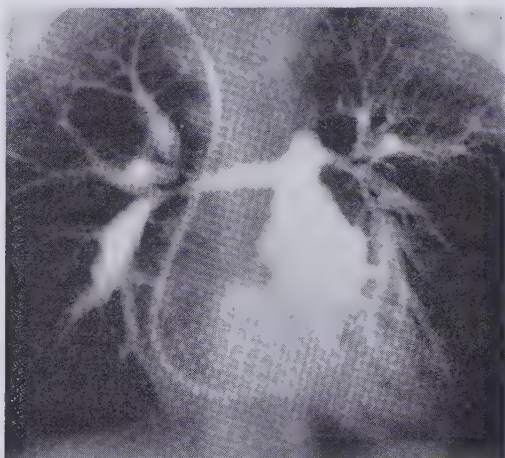


Figure 1. Preoperative angiocardigram.

* An excellent report of the patient has now appeared: Smith, G. W., Thompson, W. M., Jr., and Muller, W. H., Jr.: Surgical treatment of pulmonary hypertension secondary to multiple bilateral pulmonary arterial stenosis. *Circulation* 29 (Suppl. 1): 152-156 (Apr.) 1964.

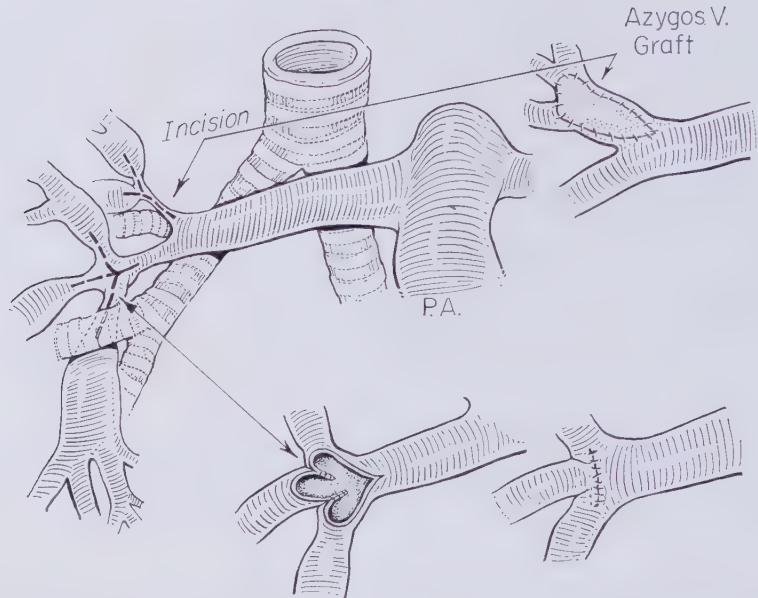


Figure 2. Technic of repair for stenosis of right upper lobe pulmonary artery and its two segmental branches, and of the intermediate artery and adjacent posterior segmental artery.

After temporary release of the clamps on the pulmonary artery, an incision in the intermediate artery was extended onto the two subdivisions of the posterior segmental artery as well as into the distal portion of the intermediate artery. A modified Heineke-Mikulicz type of plastic repair was performed at this site of stenosis in the manner illustrated (Fig. 2). Pressures following repair are indicated in Table 1. A systolic thrill was still present over the involved areas, particularly over the apical segmental branch.

Table 1. Hemodynamic Data

	PREOPERATIVE (7/25/62)	AT OPERATION			TEN DAYS AFTER OPERATION
		Before repair	After repair		
Cardiac index, L./min.....	4.2				3.2
Pressure, mm. of mercury					
Right ventricle.....	79/0				68/6
Pulmonary artery					
Main.....	75/10				67/14
Right.....	Proximal 75/5	90*	65*		
	Distal 21/-3		35-55*		
Left.....					Distal 23/12
Systemic artery.....	84/40	110*	105*		111/52

* Peak systolic pressure.

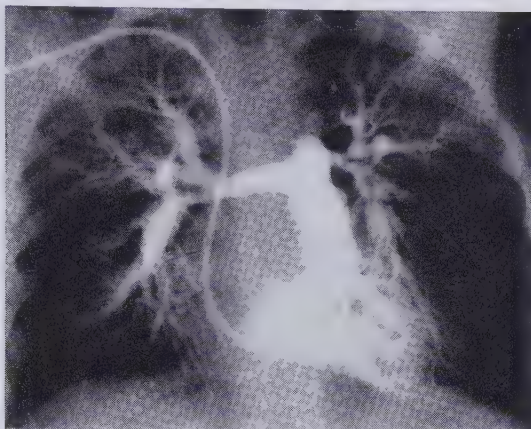


Figure 3. Postoperative angiogram.

The child made an uneventful recovery. The chest roentgenograms showed transient changes in the right upper lobe of the lung consistent with patchy pneumonitis, but this had cleared by the time of dismissal 14 days following operation. Cardiac catheterization and angiocardiography were repeated 12 days after operation. The pressure recordings are tabulated in Table 1 and the angiogram made at that time is shown in Figure 3. Two months after operation the child was well; he had gained 10 pounds and had returned to full vigorous activities without recurrence of the dyspnea and fatigue noted preoperatively.

COMMENT

The reconstruction with a patch graft seemed more satisfactory than the Heineke-Mikulicz type of repair. Pericardium is probably a better source for the patch material than the azygos vein as employed here. An accurate estimation of any benefit from this operation must await late evaluation of the result. In theory, satisfactory relief of stenosis in one pulmonary artery should effect sufficient palliation for this condition so that a future operation on the opposite side need be considered only if a strong indication should arise.

SUMMARY

Multiple sites of stenosis in the branches of the pulmonary arteries may result in significant hypertension in the main pulmonary artery and right ventricle, even in the absence of intracardiac anomalies. In the operation for this condition described, plastic reconstruction of the two principal sites of stenosis in the hilus of the right lung provided some reduction in right ventricular and pulmonary arterial hypertension and a satisfactory early symptomatic result.

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Transplantation of the Lung

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For several years the transplantation of tissues from one individual to another has been investigated both as a research procedure and as a clinical measure. In situations where vital organs have received irreversible structural damage, the therapeutic significance of surgical replacement of a diseased organ by a normal one is obvious. The lung may be affected by irreversible structural changes, and the possibility of replacement of a diseased lung by normal tissues has received consideration in conditions such as diffuse pulmonary emphysema and diffuse fibrosis. Knowledge of the principles and problems of tissue transplantation in general is necessary for consideration of lung transplantation in particular. Since detailed information concerning the basic problems of tissue transplantation may be found in several excellent reviews, including those of Medawar, Brent, Peer, Woodruff, Billingham and Silvers, and Richards, only basic general concepts will be mentioned in this summary of the current state of lung transplantation.

In the field of tissue transplantation, certain terms are commonly employed, usually according to the following definitions. An *autograft* is tissue transplanted from one location to another in the same individual. In lung-transplantation studies, reimplantation of the lung serves as the equivalent of autografting. An *isograft* (syngeneic graft) is tissue transplanted between genetically identical individuals such as members of the same sex of highly inbred strains of experimental animals or monozygotic (identical, uniovular) twins—and is, in a sense, a special form of an autograft. A *homograft* (allogeneic graft) is a graft between genetically dissimilar individuals of the same species, and a *heterograft* (xenograft) is a graft between members of different species. An *orthotopic* graft is one in which the site of origin in the donor and the site of placement in the recipient is the same while a *heterotopic* graft is one in which these sites differ. Grafts also may be subdivided on a functional basis into *homostatic* grafts, which

are not expected to survive but only to serve as a framework to be replaced by recipient tissues, and *homovital* grafts, which are expected to survive in a functioning condition.

For convenience of consideration, the problems of transplanting tissues and organs may be divided into two broad categories—which, however, are not necessarily mutually exclusive. These categories are: (1) problems of a technical nature relating to vascular and neural anastomoses (or lack thereof), the prevention of infection, and the sources and preservation of the grafts; (2) problems relating to the rejection of foreign (incompatible) tissue. While technical problems are created by all types of grafts, they have been investigated most thoroughly in conjunction with autografts or their equivalents, since homografts (and heterografts) usually* introduce the complicating factors of the rejection reaction. In the field of pulmonary transplantation the main technical problems have been considered to be: (1) the prevention of vascular thrombosis, (2) the prevention of bronchial stenosis, (3) the effects of interruption of the bronchial arterial circulation, (4) the susceptibility of the transplanted lung to infection and pulmonary edema, (5) the effects of denervation of the transplanted lung, and (6) the preservation of the lung for transplantation.

Most of these problems have been studied by lung reimplantation—which, as indicated before, is the equivalent of orthotopic autotransplantation of other organs. In dogs, unilateral reimplantation of a lung without surgical disturbance of the contralateral lung has resulted in survival of some animals for as long as 35 months^{1, 8, 14, 22-24, 26, 29, 30-32, 37, 43} with retention of function in the reimplanted lung. Thrombotic complications have been reduced by heparinization prior to removal of the lung, although hemorrhagic complications occasionally have ensued. Bronchial stenosis has been avoided by meticulous attention to surgical technique, and interruption of bronchial arteries has not resulted in subsequent bronchial necrosis. Pneumonia and other thoracic infections have not proved to be a major problem in reimplantation, nor has any unusual tendency to develop pulmonary edema been observed. Studies of pulmonary function have shown a pattern of ventilation either essentially unaltered or slightly depressed, but oxygenation of the blood has been observed to be decreased significantly. Nigro and co-workers^{31, 32} found pulmonary arterial pressure to be elevated after reimplantation, but Yeh and associates did not observe pulmonary hypertension unless atelectasis occurred secondary to bronchial stenosis.

In assessing the adequacy of the reimplanted lung alone to support life, various procedures have been carried out on the contralateral

* Certain tissues (such as those obtained from fetuses and some endocrine tissues) may not stimulate the homograft reaction. Certain sites in the recipient, notably the anterior chamber of the eye, the hamster cheek pouch, and the brain, may permit survival of homografts. In certain disease states—especially hypogammaglobulinemia, and, to a lesser degree, uremia and Hodgkin's disease—there may be lessened homograft immunity.

lung:^{1, 8, 14, 31, 32, 43} (1) contralateral pneumonectomy (which procedure also creates a situation of total pulmonary denervation); (2) contralateral pulmonary-artery ligation; (3) contralateral reimplantation; (4) contralateral multiple lobectomies with conservation of some contralateral lung tissue; and (5) contralateral lobectomy with cicatricial stenosis of the remaining bronchus. The usual outcome of the first three procedures has been death of the animals due to pulmonary edema, pulmonary hypertension with acute right-heart failure, or failure to resume spontaneous respiration. These observations, together with the findings from a greater number of survivors of the latter two procedures, have suggested that complete denervation, complete interruption of the bronchial arteries, or complete lymphatic interruption may preclude spontaneous respiration and essential functional adjustments in the pulmonary vascular bed.

On the other hand, it must be emphasized that there have been at least two instances of the survival of dogs for several days after reimplantation and contralateral pneumonectomy,^{8, 43} and two instances have been reported of survival for several days following homotransplantation of one lung with contralateral pneumonectomy.¹⁸ Furthermore, preliminary observations by Payne have suggested that in the dog the apparent inability of the autotransplanted lung to support life after contralateral pneumonectomy may be due more to technical factors of bronchial anastomosis and re-expansion of the lung in this species than to specific alterations in pulmonary physiology resulting from denervation, interruption of bronchial arterial supply, or interruption of lymphatics. Moreover, Haglin and associates have succeeded in obtaining the survival of 11 of 20 baboons for periods up to two years following reimplantation of one lung and contralateral pneumonectomy. Hence, it has been difficult to assess definitely the effects of complete denervation or interruption of bronchial arterial supply or interruption of lymphatics on pulmonary function.

So far as we know, preservation of the lung prior to reimplantation has not received extensive study.

It is apparent that in respect to the lung, the technical problems related to transplantation have not been surmounted completely in experimental animals. Important to remember, however, is that in clinical situations only unilateral transplantation would be performed. Since unilateral reimplantation may be carried out successfully, experimental investigations of homovital homografts of the lung have been pursued. Such experiments present, in addition to the technical problems already discussed, the problems of the homograft rejection reaction and its control.

It is probable that the homograft rejection reaction is basically similar for most organs and tissues; and since the reviews already mentioned^{3, 9, 28, 35, 39, 42} describe and discuss this reaction in detail, only a brief general outline will be given here. Homograft rejection has been shown to be an immunologic phenomenon in which both cellular and humoral factors may participate, although the cellular factor has been

emphasized.^{3, 6, 9, 16, 28, 35, 39, 40-42} Assuming no technical problems, a homograft in a normal recipient will appear healthy initially for a period varying from species to species—and, perhaps, from tissue to tissue—and then will undergo necrosis as it is rejected (the primary response). A second graft between the same individuals will be rejected more quickly (the second-set reaction).

Experimental attempts to modify or abolish the homograft reaction have included: (1) the induction of tolerance to the graft antigens by exposure of the recipient to them during periods of immunologic unresponsiveness or immaturity, which have been shown to occur during the intrauterine and, in some animals, the early neonatal period; (2) in certain species, preliminary thymectomy in the recipient in the early neonatal period; (3) the production of immunologic paralysis in the recipient; (4) the alteration of the graft antigens by physical means; (5) the prevention of contact between the cells of the recipient and the graft; (6) the suppression of the recipient's immunologic mechanisms by the use of x-irradiation or by chemical means. Each of these attempts has resulted in some prolongation of homograft survival or some change in the rejection reaction in some experimental animal, although a technique that is successful in one species may not be applicable to another species.

In clinical practice x-irradiation or drugs, or both, have been used in attempts to suppress the host's (recipient's) immunologic mechanisms and thus to prolong the survival of homografts. Both total-body and regional irradiation have been employed. The drugs that have been used most widely include urethan, mechlorethamine (nitrogen mustard), methotrexate (Amethopterin), 6-mercaptopurine, actinomycin C, chlorambucil, cyclophosphamide, azathioprine (Imuran), and cortisone preparations. It should be noted that for various reasons the prolonged survival of a homograft theoretically may result in loss of immunologic response by the recipient of the graft, so that the use of control measures eventually could cease. Pierce and Varco, among others, have observed continued survival of a renal homograft in a dog 10 months after cessation of immuno-suppressive therapy.

Some prolongation of the survival of the homotransplanted lung in dogs has been achieved by the use of x-irradiation and various drugs.^{2, 4-6, 10, 11, 13, 15, 18, 19, 21-23, 25, 29, 30, 33, 38} Among the drugs used, Imuran has given indications of being somewhat superior to others for reasons which, as yet, remain obscure. As would be expected, these homotransplantation studies have entailed technical problems similar to those encountered in the reimplantation experiments. Additionally, however, in contrast to the reimplanted lung the homotransplanted lung appears to be susceptible to infection, which has complicated the histologic interpretation of the homograft rejection reaction.¹² In one homograft study⁷ investigating techniques for preservation of lung prior to transplantation, reasonable success with short-term (18-28 hours) preservation was achieved by per-

fusion with CO₂-free serum at 4° C. and ventilation of the bronchus with air.

At this time (October, 1963), homotransplantation of the lung in humans has been attempted twice to our knowledge. Hardy and associates* transplanted a fresh cadaveric lung to an emphysematous man with a nonfunctioning, carcinomatous lung. Cobalt⁶⁰ therapy and Imuran were given postoperatively and the patient's pulmonary function improved. Magovern and Yates, for a homotransplant to a comatose emphysematous individual, used a fresh cadaveric lung from an individual who had been maintained in a hypothermic state for therapeutic reasons prior to death. The recipient received methotrexate and antibiotics and improved initially but died eight days after surgery. Since one lung was transplanted and the recipient's other lung was left intact, these attempts at homografting were similar to the unilateral reimplantation experiments in which the contralateral lung was not disturbed.

SUMMARY AND CONCLUSIONS

The current state of transplantation of the lung has been reviewed. Although the general principles of tissue transplantation probably are the same for most tissues and organs, in the case of lung transplantation certain technical problems have required special attention. These problems, which usually have been studied by autotransplantation (reimplantation) of the lung, include vascular thrombosis, interruption of bronchial arteries, pulmonary edema, denervation of the lung, and bronchial stenosis. Most have been resolved; but for reasons not fully understood, it remains uncertain that the autotransplanted lung alone can support life in most instances, at least in the dog. Since, however, good function of one reimplanted lung has been achieved experimentally on occasions for long periods, unilateral homografting of lung might be feasible if the homograft rejection reaction could be controlled. Experimental studies have indicated prolongation of the survival of homografted lungs by the use of x-irradiation or drugs similar to those used in other tissue and organ homograft studies, but donor sources and methods of preservation present major problems in the field of lung transplantation.

* Since preparation of this manuscript, a complete report of one patient who had unilateral homotransplantation of the lung has been published: Hardy, J. D., Webb, W. R., Dalton, M. L., Jr., and Walker, G. R., Jr.: Lung homotransplantation in man: Report of the initial case. *J.A.M.A.* 186: 1065-1074 (Dec. 21) 1963.

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